Exhibit 88

General Causation Expert Report of KATHLEEN M. GILBERT, PHD

TCE and Kidney Cancer

Prepared by:

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Contents

I. INTRODUCTION

I was asked to provide opinions concerning the likelihood that trichloroethylene (TCE) exposure contributed to the development of kidney cancer in individuals who lived and/or worked at the Camp Lejeune Marine Base in North Carolina between 1953 and 1987. A summary of my qualifications as relevant to this report is described below, while my complete CV can be found in Appendix A. My previous trial and deposition testimony experience has been limited to one previous trial testimony, one hearing and eight depositions in unrelated cases (see Appendix B). If called as a witness, I could and would competently testify to the matters set forth in this report. All of my opinions are expressed to a reasonable degree of scientific certainty, and I reserve the right to amend these opinions should new information be made available to me. I may also provide supplemental opinions regarding this case if requested.

The contaminants of interest at Camp Lejeune include TCE, perchloroethylene (PCE), vinyl chloride and benzene. These toxicants were present in the drinking water from approximately 1953 to 1987. My report will focus on TCE since that is the contaminant that has been the nexus of my own research. However, other contaminants will be discussed as sources of added toxicity.

II. BACKGROUND AND QUALIFICATIONS

My qualifications as an expert witness stem from more than 35 years of experience as a scientist conducting bench research in the areas of immunology, immunotoxicology and human health toxicology. I have been funded by the National Institutes of Health (NIH) and the Environmental Protection Agency (EPA) to study the health impacts of adult and developmental exposure to TCE. I also received $1.5 million in grant money from the Arkansas Biosciences Institute for developing an Immunotoxicology Center in Arkansas. Based on my expertise I have been asked to review grants for the National Science Foundation, the EPA, and several study sections of the NIH, including the Superfund Basic Research (ZES1 LWJ-M), and Career Award Applications for the National Institute of Environmental Sciences.

I retired from the University of Arkansas for Medical Science (UAMS) as a tenured NIH-funded Full Professor in 2017. My work at UAMS was preceded by positions at The Scripps Research Institute in La Jolla, CA; the National Institute for Medical Research in London, UK; and Memorial Sloan-Kettering Cancer Center in New York, NY.

I have published 13 book chapters, and over 80 peer-reviewed publications, more than 30 of which are directly concerned with the health effects of TCE or its metabolites. Those publications examined:

- How TCE exposure at different life stages (fetal, early life, or adult) impacts its toxicity.[4-9]
- How TCE exposure impacts the immune system at the disease, tissue, cellular, genetic and epigenetic level.[4, 10-20]
- How co-exposure to other chemicals or life-style risk factors impacts TCE-induced toxicity.[9, 21]
- How TCE causes neurotoxicity.[6, 7]
- How TCE exposure alters the gut microflora in ways that may promote systemic toxicity.[22]

- How mathematical modeling can be used to examine TCE-induced immunotoxicity.[23]

My research on TCE-induced health effects is well regarded in the scientific community. For example, I was asked by the publishers of Springer/Humana Press to edit the 2014 book entitled *Trichloroethylene: Toxicity and Health Risks*, (Springer/Humana Press New York/Heidelberg). Springer/Humana Press has published a series of excellent books on how environmental toxicants impact human health. They are used to provide reliable information for the professional practice of environmental and natural scientists, as well as human and veterinary medicine.

In recognition of my expertise in TCE toxicity and human health I have been asked several times over the years by different federal agencies including the National Research Council, the National Academy of Sciences, and the NIH's National Toxicological Program to review various TCE-related health risk documents. These included: *Assessing the Human Health Risks of Trichloroethylene: Key Scientific Issues*, 2006; *USEPA TSCA Workplan Chemical Risk Assessment for Trichloroethylene: Degreaser and Arts/Crafts Uses,* 2013*;* a possible change in listing status for TCE in the *Report on Carcinogens*, 2014; and *DOD's Approach to Deriving an Occupational Exposure Level for Trichloroethylene,* 2019.

Lastly, I was nominated for and subsequently accepted a position as one of the founding members of the Scientific Advisory Committee on Chemicals (SACC) for the EPA from 2017 to 2021. The SACC is tasked with providing independent advice and expert consultation on issues related to the implementation of the Frank R. Lautenberg Chemical Safety for the 21st Century Act which amends the Toxic Substances Control Act (TSCA). We reviewed EPA risk evaluations for 10 chemicals between 2017 and 2021 including: **TCE**, **PCE,** carbon tetrachloride, methylene chloride, 1-bromopropane, n-methyl pyrrolidone, 1,4-dioxane, pigment violet 29, and cyclic aliphatic bromide cluster. I was tasked with providing opinions on the EPA's assessment of the human health effects of these chemicals.

A more comprehensive summary of my qualifications is set forth in my CV.

For preparing this report I have invoiced my time at the rate of $400/hour. For deposition and trial testimony my hourly rate is $500/hour.

III. MATERIALS USED TO FORM OPINIONS

During my many years working with TCE, I have read hundreds of studies concerning the health outcomes of TCE exposure, as well as studies that examined the relevant modes of action. My opinions about TCE toxicity are based in part on that cumulative literature review.

Since it would be impossible for me to list all the manuscripts that I have read over the many years I have worked with TCE, the references cited in this report should be considered representative rather than exhaustive, and I reserve the right to call upon my exhaustive research and experience with TCE literature should I be called to testify in this case.

In addition to peer-reviewed published manuscripts, I also relied on the following federal reports:

> *US EPA's Toxicological Review of Trichloroethylene* of 2011. https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0199tr/0199tr.pdf

Addendum to the Toxicological Profile for Trichloroethylene published by the Agency for Toxic Substances and Disease Registry in 2013.
https://www.atsdr.cdc.gov/toxprofiles/tce_addendum.pdf

Morbidity study of former Marines, employees, and dependents potentially exposed to contaminated drinking water at US Marine Base Camp Lejeune; Agency for Toxic Substances and Disease Registry, April 2018.
https://www.atsdr.cdc.gov/sites/lejeune/docs/health_survey_report-508.pdf

The importance of animals in the science of toxicology: Society of Toxicology Animals in Research Public Policy Statement, 1999
https://www.toxicology.org/pubs/docs/air/AIR_Final.pdf

US EPA's Final Risk Evaluation for Trichloroethylene (CASRN: 79-01-6) November 2020
https://www.epa.gov/sites/production/files/2020-11/documents/1._risk_evaluation_for_trichloroethylene_tce_casrn_79-01-6.pdf

US EPA's Final Risk Evaluation for Perchloroethylene (Ethene,1,1,2,2-Tetrachloro) (CASRN: 127-18-4) December, 2020. Final Risk Evaluation for Perchloroethylene CASRN:127-18-4 (epa.gov)

ATSDR Assessment of the Evidence for the Drinking Water Contaminants at Camp Lejeune and Specific Cancers and Other Diseases
https://www.atsdr.cdc.gov/sites/lejeune/docs/atsdr_summary_of_the_evidence_for_causality_tce_pce_508.pdf

US EPA's 2023 Trichloroethylene: Regulation Under the Toxic Substances Control Act
https://www.govinfo.gov/content/pkg/FR-2023-10-31/pdf/2023-23010.pdf

Contaminated water supplies at Camp Lejeune. Assessing potential health effects
https://nap.nationalacademies.org/download/12618

Risk Evaluation for Perchloroethylene (Ethene,1,1,2,2-Tetrachloro-)
file:///C:/Users/gilbe/Downloads/EPA-HQ-OPPT-2019-0502-0058_CONTENT.PDF

Toxicological Profile for Vinyl Chloride
https://www.atsdr.cdc.gov/ToxProfiles/tp20.pdf

Public health assessment for Camp Lejeune drinking water US Marine Corps Base Camp Lejeune, North Carolina https://stacks.cdc.gov/view/cdc/43951

Toxicological Profile for Benzene https://www.epa.gov/sites/default/files/2014-03/documents/benzene_toxicological_profile_tp3 3v.pdf

IV. PROCESS USED TO FORM OPINIONS

The opinions described in this report are based upon my education, training and experience and were all made to a reasonable degree of scientific certainty. My opinions were arrived at using the same

methodology I employ in other projects such as conducting TCE research, preparing peer-reviewed manuscripts, writing research grants and assessing federal regulatory documents and making causal determinations between toxicants and diseases in other contexts.

In brief, my opinions are based on:

- Thirty-five years of experience as an immunologist, and 25 years of experience as an immunotoxicologist and human health toxicologist. This includes a well-developed understanding of correct scientific principles and methodologies.

- My own extensive peer-reviewed and NIH-funded research on TCE and disease outcomes.

- Experience on the SACC that included my invited professional review of the *EPA 2020 Risk Evaluation for Trichloroethylene*[2] and the *EPA 2020 Risk Evaluation for Perchloroethylene*.[26]

As identified above, my causation opinions for TCE are in part informed by the evaluation conducted by the EPA in its 2020 *Risk Evaluation for Trichloroethylene* and the ATSDR in its A*ssessment of Evidence for the Drinking Water Contaminants at Camp Lejeune and Specific Cancers and Other Diseases*.[2, 27] As discussed in greater detail throughout my report, I independently assessed the sources relied upon by these agencies in reaching my opinions in this case and performed my own independent analysis.

As is standard practice for experts I have chosen to use a weight-of-evidence (WOE) approach to the opinions in this report. To form their causation opinions both agencies (EPA and ATSDR) used a weight-of-evidence (WOE) approach. The WOE is defined as "*a systematic review method, applied in a manner suited to the nature of the evidence or decision, that uses a pre-established protocol to comprehensively, objectively, transparently, and consistently identify and evaluate each stream of evidence, including strengths, limitations, and relevance of each study and to integrate evidence as necessary and appropriate based upon strengths, limitations, and relevance.*" (https://epa.gov/sites/default/files/2018-06/documents/final_application_of_sr_in_tsca_05-31-18.pdf) The EPA WOE approach integrates data from epidemiological studies, animal studies and mechanistic studies.

To meet the TSCA science standards for the literature reviews included in their reports, EPA used the TSCA systematic review process described in the *Application of Systematic Review in TSCA Risk Evaluations* (https://19january2021snapshot.epa.gov/sites/static/files/2018-06/documents/final_application_of_sr_in_tsca_05-31-18.pdf). This process complements the Risk Evaluation process in that the data collection, data evaluation and data integration stages of the systematic review process are used to develop the exposure and hazard assessments based on reasonably available information.

It is important to note that the analysis conducted by the EPA does not represent the opinion of a single individual or a single agency. As required by TSCA, the EPA 2020 *Final Risk Evaluation for Trichloroethylene* [2] was reviewed by the members of the SACC. This committee contains wide-ranging expertise, including risk assessors, epidemiologists, statisticians, toxicologists, and industry representatives. I was one of the SACC members that participated in the review of TCE. The evaluation was held in a public meeting in which anyone could register to make comments. Cumulatively, dozens of scientists and non-scientists weighed in on the evaluation and general consensus was reached regarding

TCE causation. For these reasons, it is my opinion that the methodology used by the EPA and ATSDR, and which I describe here, are carefully reasoned and scientifically valid.

The causation evaluations conducted by the EPA and ATSDR were based on modified Bradford Hill Considerations. In 1965 Professor Hill gave a talk in which he described nine "viewpoints" to consider while determining disease causation.[28] This list included temporality of exposure, strength of exposure, dose-response determination, plausibility, elimination of alternative explanations, consistency/reproducibility, experiment (e.g. alleviation of toxicity by preventing or removing exposure), coherence, and specificity. These common-sense considerations are not a strict checklist. Professor Hill himself says "None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*." Although the Bradford Hill considerations as a framework for critical thinking continues to be very useful, the field of toxicology has evolved to include new technologies and new fields of study (e.g. molecular toxicology). A modified Bradford Hill approach reflects these changes and is more comprehensive in its inclusion of all applicable data (animal studies, *in vitro* studies and epidemiological studies).

Similar to the EPA and the ATSDR I used a modified Bradford Hill approach to derive my opinions. This means I included results from epidemiological, animal and mechanistic (sometime *in vitro*) studies. The importance of these three components in determining a causal relationship will be described below.

With respect to the causation standard I employed in reaching my opinions, I have reviewed the Camp Lejeune Justice Act (CLJA) and am aware the causation standard under the CLJA explains that Plaintiffs in this case must show "the relationship between exposure to the water at Camp Lejeune and the harm is—(A) sufficient to conclude that a causal relationship exists; or (B) sufficient to conclude that a causal relationship is at least as likely as not." *ATSDR Assessment of Evidence*, referenced above, considers the "at least as likely as not" standard to be the functional equivalent of its category for "equipoise and above." Although my opinions in this case are expressed to the higher "more likely than not" standard, the ATSDR's definition of "equipoise and above" served as a guidance for me in this case. These classifications and categories are consistent with my education, training and experience and with the sciences to which they relate.

A. Importance of epidemiological studies

Epidemiological studies examine the direct real-life relationship between exposure to a particular toxicant and a particular toxicity. They are very useful in providing proof of concept that exposure to a particular toxicant is associated with a specific pathology. This approach is obviously relevant for human risk evaluation and circumvents the need to extrapolate animal or *in vitro* exposure levels to human equivalence.

If epidemiology studies do exist and provide relevant information, they are often looked at as the highest potential level of evidence in determining these causal relationships. However, epidemiology studies are sometimes limited in terms of documenting precise toxicant exposure, and in terms of providing different tissues and cell types for confirmatory mechanistic information. They also often examine occupational rather than environmental exposure because the former is far easier to document. If someone encounters a toxicant outside of the workplace, they are often unaware of it. And in many cases, including Camp Lejeune, people are often unaware of their environmental exposures until many

years later, if ever. Thus, human studies are augmented by animal and *in vitro* models, which can circumvent some of the limitations of epidemiological studies.

B. Importance of animal studies

As stated in the Society of Toxicology Animals in Research Public Policy Statement:

> "In the absence of human data, research with experimental animals is the most reliable means of detecting important toxic properties of chemical substances and for estimating risks to human and environmental health." https://www.toxicology.org/pubs/docs/air/AIR_Final.pdf
>
> *"If there is sufficient human data to describe the exposure-response relationship for an adverse outcome(s) that is judged to be the most sensitive effect(s), reference values should be based on human data. If sufficient human data are not available, data from animal studies must be employed with appropriate interspecies and intraspecies extrapolation factors."* https://www.epa.gov/sites/production/files/2015-01/documents/ddef-final.pdf

Animal models have many advantages when examining chemical toxicity:

- Toxicant exposure can be carefully administered and monitored. This makes it easier to evaluate dose-dependent and time-dependent effects. *Such studies would obviously be unethical in humans.*

- Animal models can evaluate the effects of toxicant exposure on specific life stages (i.e., infants and the elderly).

- Animal models have advantages over the use of cultured cells, even if human in origin, to study toxicity. For example, any disease, such as kidney cancer, with an immune system component involves multiple cellular interactions. It is currently impossible to mimic these interactions using individual populations of cultured cells. Instead, a sophisticated physiological system, such as can only be found in an intact animal, is needed to recapitulate complex diseases such as cancer.

Mice and humans share over 90 percent of the same genes, and are strikingly similar in terms of anatomy, physiology, and drug metabolism. It is undeniable that information obtained in mouse models is very often relevant to humans. For example, immune-based cancer vaccines and new cancer therapeutics known as immune checkpoint inhibitors, which are widely used to treat many types of cancer, were initially developed in mouse models before being successfully translated into human clinical trials.

It is also relevant to note that the vast number of chemicals identified in the environment or introduced as commercial products have never been tested for carcinogenicity. Unlike clinical trials that test chemicals with intended therapeutic value, testing these other chemicals for their carcinogenicity in humans has long been considered unethical.

Thus, animal models, especially mouse models, recapitulate human systems very well, and are often used to estimate the effects of a toxicant on human health. Many of the recent improvements in the care of patients with kidney disease and cancer have resulted from basic research conducted using

laboratory animals. For example, immune-based cancer vaccines and new cancer therapeutics known as immune checkpoint inhibitors that are crucial for the treatment of kidney cancer were initially developed in mouse models before being successfully translated into human clinical trials.

C. Importance of mechanistic studies

In addition to information obtained from epidemiological studies and animal models, mode of action (MOA) evidence is important to a WOE causation determination. The EPA and other governmental agencies agree with this methodology. Defining MOA (sometimes called mechanism of action or adverse outcome pathway) means identifying key events between exposure and pathology. Mechanistic research elucidates the cellular, biochemical, and molecular basis of chemical toxicity. The EPA's 2014 *Framework for Human Health Risk Assessment to Inform Decision Making* discussed the importance of identifying MOA in the risk assessment process.

https://www.epa.gov/sites/default/files/2014-12/documents/hhra-framework-final-2014.pdf

Understanding the MOA can inform causal relationship by:

(i) Supporting a designation of causation

(ii) Confirming relevance of data in animals or *in vitro* for human health risk assessment

(iii) Harmonizing causal relationship for various health endpoints

(iv) Defining conditions under which a chemical is likely to cause an adverse effect

(v) Helping to generate pharmacologic and nonpharmacologic strategies to counteract the adverse outcomes of chemical exposure.

Lastly, mechanistic information uncovered while studying a specific toxicant can help unravel complex mechanisms of disease onset and progression and define the role of environmental insult in idiopathic disease.

Defining MOA often uses complimentary toxicokinetic and toxicodynamic evaluations.

Toxicokinetics includes information about the absorption, distribution, metabolism, and excretion of a toxicant. Toxicokinetic data for many chemicals are determined by using PBPK (physiologically based pharmacokinetic) modeling. This is a widely used and widely accepted mathematical modeling technique for predicting the absorption, distribution, metabolism and excretion of toxicants in humans and other animal species. PBPK models can be used to convert animal exposures into human equivalent exposures.

Toxicodynamics defines the processes by which a toxicant, once it has been absorbed, distributed and metabolized, interacts with the body to cause adverse effects. Toxicodynamic data is derived from human, animal and *in vitro* studies. MOA data from human subjects is most often derived from blood samples since examination of other tissues is often logistically and ethically problematic. Unlike human exposure, animal models greatly expand the types and numbers of samples (blood and multiple tissues) that can be collected and examined. The EPA also uses mechanistic data derived from *in vitro*

experiments (some of which use human cell types as targets) when synthesizing evidence for causation.

V. SUMMARY OF KIDNEY CANCER ETIOLOGY

The discussion of how TCE promotes kidney cancer will be prefaced by a brief description of the disease. In the US kidney cancer is the 6th most common cancer in men, and the 9th most common in women. Less than 10% of kidney cancer cases appear to involve a genetic predisposition https://www.cancer.gov/types/kidney/hp/renal-cell-carcinoma-genetics#_4 Thus, the major triggers for kidney cancer can be said to be environmental. Toxicant exposure is a known cause and risk factor for tumorigenesis and the development of kidney cancer. Some other known risk factors for kidney cancer include smoking, obesity and hypertension.[29] However, these risk factors account for much less than 50% of cases, thus making it clear that other environmental factors, such as toxicant exposure, must play a role in tumorigenesis. https://www.cancer.gov/types/ kidney/hp/ renal-cell-carcinoma-genetics#_4

In terms of etiology it is clear that many of the hallmarks of kidney cancer including tumor cell proliferation, migration, angiogenesis and metastasis are mediated by inflammation.[30] This inflammation encompasses several pathways including increased production of pro-inflammatory cytokines such as IL-6, TNF-α and IL-1β.

Closely related to inflammation is oxidative stress, which can be either causal or secondary to inflammation. Oxidative stress also plays a major role in cancer development where it can promote initiation, angiogenesis, invasiveness, and metastasis.[31] Dysregulation of oxidative stress plays an important role in the carcinogenesis and progression of kidney cancer.[32, 33]

In addition to generalized inflammation and oxidative stress, kidney cancer is also associated with suppression of anti-tumor-specific T cells. This has been correlated with decreased IFN-γ-secreting T cells in the blood and tumor of patients with kidney cancer. [34, 35] IFN-γ is a pleiotropic cytokine with multiple biological effects, one of which is a direct cytotoxic effect on tumor cells. The functional importance of the T cell immune suppression found in kidney cancer is underlined by the fact that most treatments for kidney cancer target the immune system by stimulating effector T cells and/or blocking the ability of the tumor to inhibit T cell activity.[36]

Opinions 1 and 2 will present evidence that TCE causes kidney cancer and induces many of the inflammatory and immunosuppressive endpoints found in idiopathic kidney cancer.

VI. OPINION 1. TCE CAUSES KIDNEY CANCER

This causation determination is based in part on epidemiological studies, animal studies, mechanistic studies, and the conclusions of federal agencies such as the EPA, IARC and ATSDR.

A. Epidemiological studies

Epidemiology studies clearly indicate that TCE causes kidney cancer and serve as strong support for the conclusion that the levels of TCE at Camp Lejeune were hazardous to humans generally and known to cause kidney cancer. Based on the weight-of-evidence approach, the information from these epidemiology studies weighs heavily in favor of this causal relationship. This is even stronger under the standard “as likely as not” in this case.

According to the ATSDR the evidence is sufficient to conclude that a causal relationship exists if (a) There is sufficient evidence from human studies (a meta-analysis and/or by several studies considered to have high utility) in which chance and biases (including confounding) can be ruled out with reasonable confidence, or (b) There is less than sufficient evidence from human studies but sufficient evidence in animal studies and strong evidence that the agent acts through a relevant mechanism in humans. The ATSDR did not use statistical significance as part of the assessment process.

Further, ATSDR's Assessment of the evidence from 2017 lists different ways in which the standards for "Sufficient evidence for causation" and "Equipoise and above evidence for causation," can be met. For example, ATSDR states,

> Sufficient evidence for causation: the evidence is sufficient to conclude a causal relationship exists. This category would be met, for example, if:
>
> 1. There is sufficient evidence from human studies in which chance and biases (including confounding) can be ruled out with reasonable confidence, or
>
> 2. There is less than sufficient evidence from human studies but sufficient evidence in animal studies and strong evidence that the agent acts through a relevant mechanism in humans.
>
> Equipoise and above evidence for causation: The evidence is sufficient to conclude that a causal relationship is at least as likely as not, but not sufficient to conclude that a causal relationship exists. This category would be met, for example, if:
>
> 1. The degree of evidence from human studies is less than sufficient but there is supplementary evidence from animal studies and/or mechanistic studies that supports causality, or
>
> 2. A meta-analysis does not provide convincing evidence (e.g., the summary risk estimate is close to the null value of 1.0, i.e., $\leq$ 1.1), or if the meta-analysis observes a non-monotonic exposure-response relationship) but there is at least one epidemiological study considered to be of high utility occurring after the meta-analysis has been conducted, in which an association between the exposure and increased risk of the disease of interest has been found and in which chance and bias can be ruled out with reasonable confidence.
>
> 3. A meta-analysis has not been conducted, but there is at least one epidemiological study considered to be of high utility in which an association between the exposure and increased risk of the disease of interest has been found and in which chance and biases can be ruled out with reasonable confidence.

I began my epidemiological review of TCE by reviewing those studies identified by the 2017 ATSDR Assessment of the Evidence. I also reviewed the EPA 2020 Risk Evaluation of Trichloroethylene which included epidemiological studies that had been published between 2017 and 2020. Both the ATSDR and the EPA have defined systemic review methodology used to determine whether a study (i) meets basic criteria that makes it eligible for consideration, and (ii) provides reliable and useful information.[37] https://www.epa.gov/sites/ default/files/2015-07/documents/lit-studies.pdf. [27]I found the ATSDR's and

EPA's methodology for reviewing the epidemiology to be thorough and scientifically-valid based on my years of experience and training as a scientist. Lastly, I used PubMed (the free online NIH-sponsored database of medical science studies) to identify epidemiological studies published between 2020 and 2024. Any new federal reports or regulatory documents published since 2020 were also included in my literature search.

For inclusion in the epidemiological assessment of kidney cancer shown here studies had to demonstrate (1) a temporal relationship between chemical exposure and negative health effect (i.e. exposure precedes toxicity) and (2) convincing positive associations represented by a Risk Ratio (RR), Odds Ratio (OR), Standardized Mortality Ratio (SMR), or Standardized Incident Ratio (SIR) greater than 1.1, and (3) adult exposure of more than one month duration. This is consistent with sound scientific principles, especially considering the lower standard of proof "as likely as not" being used in this case.

Once those basic requirements have been met epidemiological studies were further assessed to best identify those studies with the highest utility. Pursuant to my methodology, which is consistent with ATSDR standards, I evaluated the studies for:

1. **Proper Controls**. Data quality in epidemiological studies requires the use of proper controls. For example, it would be more appropriate if the results obtained from Marines exposed to TCE at Camp Lejeune were compared to non-exposed Marines at another base who might be expected to have a similar fitness baseline as compared to potentially less healthy civilians.

2. **Confounding bias.** All the studies presented here were evaluated for whether possible confounding variables such as exposure to smoking or other risk factors were taken into account.

3. **Exposure assessment**. Most of the occupational exposure studies used some kind of Job Exposure Matrix (JEM) to estimate TCE exposure. As noted, some studies used actual on-site measurements or bio-monitoring to estimate exposure.

4. **Likely exposure.** Exposure miscalculation can be lessened if the results were observed in the population determined to be the most likely to be exposed to the highest concentrations of TCE or exposed for the longest duration. These values were used here.

5. **Dose-duration relationship.** Since an exposure-response relationship adds extra weight in risk determination all the studies described here were evaluated for this criterion.

6. **Incidence vs mortalit**y. The ATSDR gives weight to those studies that examined incidence rather than mortality.

7. **Meta-analysis**. As noted by the ATSDR a meta-analysis is given extra weight since it represents the statistical analysis of multiple studies. Its pooled approach to data evaluation can lessen the biases and errors of individual studies.

The epidemiological evidence for TCE-induced kidney cancer per the ATSDR criteria is shown In **Table I** below. Included are four studies conducted for the ATSDR by Bove *et al*. which reported that both civilians and Marines who were exposed to the cumulative volatile organic compounds (VOC) in the contaminated water at Camp Lejeune had an increased mortality and morbidity rates for kidney cancer. The values represented TCE exposure unless otherwise indicated.

Table I Epidemiological evidence that TCE and other VOC cause kidney cancer

Studies	Type	OR, RR, SIR,SMR	95% CI	Exposure	Described threshold		Confounder adjustments	Dose-duration	Incidence vs Death	Meta-analysis
					Dose (ppb) or Duration (mean)	OR + 95% CI				
Andrew [38]	Environ. Case-Con	1.78	1.05-3.03	Geo-coding	0 - 25.3 5 yrs	1.47 0.9-2.4	age, smoking, BMI, diabetes		✓	
Aschengrau [39]	Environ. Case-Con	PCE 6.04	1.32-21.8	Geo-coding	Cumulative 27,100 - 44,100 µg*		Sex, smoking, age, other exposures		✓	
Bove [40] Marines 2014	Environ. Retro Cohort	VOC 1.35	0.84-2.16	Historical Measures	PEC 1-155 µg/L-months 1.4 VOC 1-4,600 µg/L-months 1.42 TCE 1-3,100 µg/L-months 1.54 VC 1-205 µg/L-months 1.66 Benzene 2-45 µg/L-months 1.69	0.54-3.5 0.58-3.5 0.65-3.6 0.68-4.0 0.73-3.9	smoking, race and rank			
Bove [41] Civilians 2014	Environ. Retro Cohort	VOC 1.92	0.58-6.34	Historical Measures			smoking, race and job			
Bove [42] 2024 Incidence	Environ. Retro Cohort	VOC Civilians 1.7 Marines 1.12	0.93-3.13 0.99-1.27	Historical Measures	1-6 quarters on base		Smoking, alcohol, age		✓	
Bove[43] 2024 Mortality	Environ. Retro Cohort	VOC Civilians 1.44 Marines 1.21	0.73-2.84 0.95-1.54	Historical Measures	1-2 quarters on base		Smoking, alcohol, age			
Bruning [44]	Occup. Case-Con	1.8	1.01-3.20	JEM, survey			age, gender, smoking			
Charbotel[45]	Occup. Case-Con	2.16	1.02-4.60	JEM			smoking, BMI	✓	✓	
Dosemeci. [46]	Occup. Case-Con	2.0 Female	1.0-4.0	JEM			age, smoking, BMI, hyper.		✓	

Henschler [47]	Occup. Retro Cohort	3.28	0.4-11.84	Specific JEM			age, BMI and smoking.		✓	
Kelsh [48]	Occup. Cohort + Case-Con	1.34	1.06-1.68	JEM, self-assess					✓	✓
Moore [49]	Occup. Case-Con	2.05	1.13-3.73	JEM	Years < 13.5 1.89 > 13.5 2.25 Intensity < 76 ppb 1.73 > 76 ppb 2.41	0.84-4.3 0.95-5.3 0.75-4.0 1.05-5.6	age, BMI, smoking	✓	✓	
Parker and Rosen [50]	Environ. Cross-section	VOC 1.88		Survey Measures	TCE 157.9 PCE 15.4					
Pesch [51]	Occup. Case-Con	1.6 Female	1.0-2.5	JEM			age and smoking	✓		
Purdue [52]	Occup. Case-Con	1.7	0.8-3.8	JEM			age, BMI, smoking		✓	
Raaschou-Nielsen [53]	Occup. Cohort	1.4	1.0-1.8	JEM					✓	
Scot, *et al.*[54]	Occup. Cohort + Case-Con	1.58	1.28-1.96	JEM			smoking			✓
Spirtas [55]	Occup. Cohort	1.20 Male	0.52-2.37	JEM						
EPA IRIS [1]	Occup. Cohort + Case-Con	1.27	1.13-1.43	JEM						✓
EPA [2]	Occup. Cohort + Case-Con	1.22	1.07-1.38	JEM			smoking			✓
Vamvakas [3]	Occup. Case-Con	TCE+ PCE 10.8	2.26-34.75	JEM			age, BMI, smoking, hypertension		✓	
Wartenberg [24]	Occup. Cohort	1.7	1.1-2.7	JEM					✓	✓
Zhao [25]	Occup. Cohort	4.9	1.23-19.6	JEM			smoking	✓	✓	

#Total PCE that entered home, only a fraction of which would have been inhaled or ingested

These epidemiology studies provide robust evidence of a causal relationship between TCE and kidney cancer. They are sufficient to conclude a causal relationship exists under a more likely than not standard and clearly are sufficient under the as likely as not standard applicable here.

B. Animal studies

A large study conducted by the NTP showed that high doses of TCE administered by gavage generated statistically significant levels of renal cancer in male F344 rats, a strain with a very low historical control incidence of renal cancer.[56] This study confirmed earlier results by the NTP in which four different strains of rats demonstrated a TCE-induced increase in the incidence of kidney cancer.[57] Given the rarity of renal tumors in these rodents and the repeatability of this result, these results were considered by the EPA as biologically significant confirmation of the epidemiological results.

This evidence provides further support of the causal relationship between TCE and kidney cancer.

C. Mechanism of action

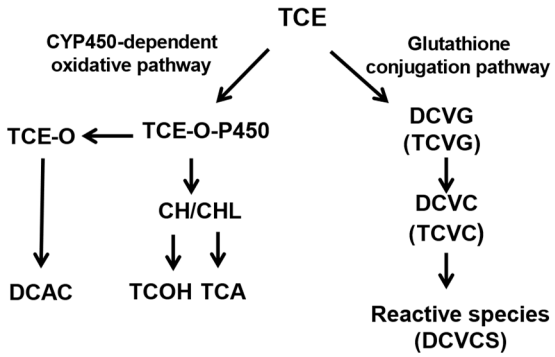
Tumorigenesis (aka carcinogenesis) is a multi-step process that starts with conferring tumor clonality, i.e. the ability of single cells to begin to proliferate abnormally. This transformation is crucial to tumor growth and is quite different from the carefully controlled and limited proliferation of normal cells. Tumor clonality is thought to require DNA-specific damage also known as genotoxicity (which may or may not involve mutagenicity). Any agent that initiates tumor growth via genotoxicity or supports subsequent tumor development is said to be carcinogenic. The mechanism for TCE genotoxicity appears to require its metabolic conversion into active metabolites.[58] [59] Consequently, the discussion of how TCE triggers cancer growth will be preceded by a brief description of TCE metabolism.

1. TCE metabolism

As a small lipophilic (fat soluble) chemical TCE can easily cross biological membranes regardless of whether exposure occurs through a dermal, oral or inhalation route. Following its absorption TCE rapidly partitions into blood by binding to soluble components such as lipids. Once in the bloodstream TCE is widely distributed throughout the body but quickly transitions to the two main sites of metabolism, the liver and the kidney.

After transitioning to the liver TCE is subject to oxidative metabolism by cytochrome P450s, most predominantly CYP2E1. The first step in the oxidative metabolism of TCE is the formation of an unstable intermediate (TCE-O-P450) that then leads to the generation of reactive metabolites chloral hydrate (CH) [aka trichloracetaldehydye hydrate (TCAH)] and chloral (CHL). CH/CHL is reduced by aldehyde dehydrogenases or P450s to trichlorethanol (TCOH) or oxidized to trichloroacetic acid (TCA). Alternatively, TCE-O-P450 can be converted to TCE-epoxide (TCE-O). TCE-O can form dichlordoacetyl chloride (DCAC),trichloracetaldehyde) **(Figure 1**).

Figure 1. TCE metabolism



The secondary pathway for TCE metabolism involves conjugative metabolism with glutathione-S-transferases (GSTs). Conjugation is a process that generally leads to detoxification. However, that is not the case for TCE and many other halogenated compounds which get converted into harmful reactive metabolites. GSTs conjugates di- and trichlorovinyl-L-glutathione (DCVG and TCVG) are formed in the liver and then transition to the kidney where they are cleaved into di- or trichlorovinyl-L-cysteine (DCVC or TCVC). These products can then be enzymatically converted to reactive metabolites DCVCS [e.g. N-acetyl-S-(1,2-dichlorovinyl)-L-cysteine) which are thought to mediate renal damage and cancer.

Most TCE metabolites from both the oxidative and conjugation pathways are ultimately eliminated in urine and feces although some proportion of absorbed TCE is exhaled as intact parent compound.

2. TCE genotoxicity

Carcinogenesis is a multi-step process that starts with conferring tumor clonality, i.e. the ability of single cells to begin to proliferate abnormally. This transformation is crucial to tumor growth and is quite different from the carefully-controlled and limited proliferation of normal cells. Tumor clonality is thought to require DNA-specific damage known as genotoxicity (which may or may not involve mutagenicity).

TCE has been labeled as a genotoxic chemical at least with regard to kidney cancer. This means that TCE can initiate the carcinogenic process. The genotoxic MOA for TCE in the kidney involves formation of the reactive GSH metabolites such as DCVC [S-(1,2-dichlorovinyl)-L-cysteine)] [2] described above. This MOA is well-supported by toxicokinetic data indicating that these metabolites are present in both human blood and urine, and these metabolites have been shown to be genotoxic both *in vitro* and in animal studies demonstrating kidney specific genotoxicity.[2] While scientific studies have yet to demonstrate a level of TCE exposure below which cancer risk goes to zero, epidemiological studies do provide evidence that TCE, at levels of exposure comparable to than those encountered at Camp Lejeune, can cause cancers, including but not limited to kidney cancer.

Although there is evidence that TCE can initiate tumor cell transformation via genotoxicity, there is also evidence that TCE can further support cancer development via the non-genotoxic immunotoxicity. These additional mechanisms will be discussed in Opinion 2.

This mechanistic explanation provides biological plausibility for a causal relationship between TCE and kidney cancer.

D. Agency conclusions regarding TCE and kidney cancer

ATSDR: Sufficient evidence for causation.[27]

EPA IRIS Toxicological Review of Trichloroethylene (2011): This report concluded that TCE is "carcinogenic to humans" based on convincing evidence of a causal relationship between TCE exposure in humans and kidney cancer. [1]

International Agency for Research on Cancer (IARC) (2014): The IARC found sufficient evidence for the carcinogenicity of TCE in humans, and definitively stated that TCE causes kidney cancer. They noted the strong consistency of the epidemiologic data on TCE and kidney cancer argues against chance, bias, and confounding as explanations for the elevated kidney cancer risks.[60]

National Toxicology Program Report on Carcinogens, Fifteenth Edition (2015): The NTP stated that epidemiological studies provide evidence of a causal relationship between TCE exposure and kidney cancer based on consistent evidence of increased risk of kidney cancer across studies with different study designs, geographical areas, and occupational settings.[61]

EPA Risk Evaluation for Trichloroethylene (2020): "In summary, meta-analyses accounting for between-study heterogeneity, influential observations, and data quality consistently indicate positive associations of NHL, kidney cancer and liver cancer with exposure to TCE. This conclusion generally agrees with that of other governmental and international organizations."

E. Summary

The designation of TCE as a carcinogen by federal and international agencies stems largely from the convincing epidemiological evidence supporting the association between TCE exposure and kidney cancer. This included meta-analyses of both cohort and case-control studies. Relative risk estimates for increased kidney cancer were consistent across a large number of epidemiological studies of different designs and populations from different countries and industries. That is not to say that all studies found an association between TCE and kidney cancer; there were a number that didn't.[2] However, the no-causation studies were far outnumbered by the studies that did demonstrate causation. Thus, as noted by federal agencies, the WOE strongly supports a causation association between TCE and kidney cancer.

This epidemiological evidence for causation has been bolstered by animal studies of TCE-induced kidney cancer, and by mechanistic studies that have identified biological plausible processes for TCE carcinogenicity in the kidney. This opinion is consistent with the conclusions of federal and international agencies.

Taken together, the weight of evidence leads to the conclusion that TCE exposure causes kidney cancer.

VII. ROLE OF IMMUNE SYSTEM IN MEDIATING KIDNEY CANCER

TCE-induced genotoxicity is not the only mechanism by which TCE promotes kidney cancer. The ability of TCE to cause immunotoxicity is also a very important contributor. Before describing how the immunotoxic effects of TCE can promote tumorigenesis (OPINION 2) the crucial role of the immune system in mediating cancer in general, and kidney cancer specifically, will be summarized.

A. Summary of Immune System

1. Importance of Immune System

The immune system is crucial for fighting infection and preventing cancer. The importance of a correctly working immune system in human health cannot be overstated. Omics technology that captures multiple longitudinal changes in the immune system can be compiled into a clinically relevant "biological clock" that accurately predicts general morbidity and mortality beyond the well-established risk factors.[62] Due to the critical role of the immune system in regulating disease outcomes it is clear that perturbation of this system, such as caused by TCE, can promote many negative health effects, including cancer.

2. Summary of immune system

The immune system is a network of cells and their soluble mediators. The cells of the immune system can be found in the circulation as well as in specific immune organs such as the spleen and lymph nodes. Anything that can trigger a response from the cells of the immune system is called an antigen. Most antigens encountered by humans are harmful foreign molecules such viral proteins, bacterial toxins, and tumor markers.

Like a good security system, the immune system is supposed to prevent intruders from accessing your home. The immune system is comprised of both "innate" and "adaptive" components. When the intruders (e.g. cancer cells) trigger your security alarm, the Innate system acts as the first stage of protection (dogs barking) while you wait for the police (adaptive immune response) to arrive. Anything that disrupts either of those protective elements can increase cancer cell access.

The innate immune system is comprised of cells such as macrophages, dendritic cells, neutrophils and natural killer cells. These cells are considered somewhat immune non-specific in that they do not have receptors that recognize specific antigens. The cells of the innate immune system travel to the site of injury (e.g. infection or tissue damage) and provide the first line of defense via the production of soluble mediators known as cytokines or chemokines.

The adaptive immune system provides the second and more specific line of defense against antigens. It is comprised primarily of B cells and T cells (which consist of CD4+ T cells and CD8+ T cells). Unlike the cells of the innate immune system, all B cells and T cells have on their surface a unique receptor specific for one particular antigen, such as a specific tumor marker. Antigen-specific B cells and T cells travel to the site of antigen introduction, guided in part by the presence of the innate system soluble mediators. Once the B cells interact with their specific antigen they begin to make antibodies, soluble proteins that bind to and destroy soluble antigens or indirectly act to promote the death of antigen-expressing cells. Antigen-triggered $CD8^+$ T cells, often called cytotoxic T cells, can kill cancer cells expressing tumor

antigens or non-cancerous cells infected by intracellular pathogens. Antigen-triggered CD4+ T cells, often called helper T cells, provide crucial support for B cell antibody production. The effector function of activated CD4+ T cells and $CD8^+$ T cells can involve direct cell-to-cell contact or the release of soluble mediators such as cytokines.

B. Immune System and Tumorigenesis

1. Immune surveillance

The innate and adaptive immune system work together to prevent cancer through a mechanism known as **immune surveillance.** Immune surveillance is an ongoing process by which the immune system surveys the body for tumors and then eliminates them. Once a cell such as a kidney cell has been transformed (e.g. by genotoxicity) into a cancer cell and begins proliferating it often upregulates tumor-specific antigens which make it a target for the immune system. Unfortunately, the targeted anti-cancer immune response is not always successful. This is due to bidirectional and sometimes flawed interactions between the immune system and cancer cells known as **cancer immunoediting**. During cancer immunoediting the host immune system shapes tumor growth in three phases, elimination, equilibrium and escape:

(a) Elimination

In the elimination phase proliferating cancer cells expressing tumor antigens are destroyed by a competent immune system. This represents a coordinated attack by the innate and adaptive immune system against cells expressing tumor antigens. The cells of the innate immune system can kill tumor cells through the release of soluble mediators (e.g. perforin and granzyme). The adaptive immune response can cause tumor cell killing directly through $CD8^+$ T cell cytotoxic mechanisms or indirectly through different CD4+ T cell-mediated mechanisms or via the generation of natural anti-tumor antibodies.

(b) Equilibrium

If not all the tumor cells are destroyed during the elimination phase of cancer immunoediting tumorigenesis may enter into the equilibrium phase. In this phase the immune system prevents the outgrowth of the tumor but is unable to eliminate all the tumor cells. Unfortunately, the selective pressure to evade elimination by the activated immune cells can drive the tumor cells to evolve through mutations or epigenetic alterations into cells with mechanisms that allow them to circumvent immune system control.

(c) Escape

The escape phase represents the final phase of tumorigenesis where the tumor cells that have developed to evade the immune system grow progressively and develop into a clinically apparent disease. This involves the establishment of an immunosuppressive microenvironment in the tumor that discourages further destruction by CD4+ and CD8+ T cells.

2. How immune surveillance goes wrong during development of kidney cancer

(a) Chronic inflammation

In order for the immune system to work correctly to fight infection or prevent cancer the innate and adaptive immune system must maintain a delicate balance of immune activation and deactivation. Temporary inflammation is a crucial part of the immune response to antigen and subsequent tissue repair. The immune response is supposed to be proportional to the threat, and to subside once the threat has been resolved. However, when the immune response is not resolved (cancer is not eliminated) or when the innate immune system is artificially stimulated by extrinsic factors it can lead to a sustained state of **chronic inflammation** that is more harmful than protective. Chronic inflammation has been shown to be a contributing factor to cancer, cardiovascular disease, diabetes and other metabolic diseases, chronic kidney disease, and neurodegenerative disorders.[63]

Chronic inflammation is an important component of kidney cancer and provides support for tumor progression, metastasis and anti-cancer resistance [30]. Inflammation in kidney cancer is mediated in large part by soluble factors such as IL-6, IL-1β and TNF-α. All three of these soluble factors are considered pro-inflammatory cytokines that are made by macrophages of the innate immune system, and which can also be generated by kidney cancer cells and other cells in the tumor microenvironment (TME).[30] Increased levels of these pro-inflammatory cytokines, whether in the TME or serum correlate with renal cancer recurrence and progression. All three can initiate signaling that promotes tumor proliferation, survival, immune evasion and/or metastasis.[64] The functional importance of these cytokines in mediating kidney cancer is underlined by the fact that treatments that block these factors (usually immunotherapeutic monoclonal antibodies) have been shown to be effective in clinical trials[65], or in mouse models of kidney cancer.[66]

Thus, the weight of evidence suggests that increased production of IL-6, IL-1β and/or TNF-α promotes chronic inflammation that in turn promotes growth of kidney cancer. The ability of TCE to increase the levels of these pro-inflammatory pro-tumorigenic cytokines will be described in Opinion 2.

(b) Immunosuppression of adaptive immune response

Aside from inflammation caused by cells of the innate immune system, suppression of cancer-specific CD4+ and CD8+ T cells is also a crucial part of kidney cancer tumorigenesis. [67] A recent study of 80 renal cancer patients showed that compared to healthy controls, patients with kidney cancer had lower percentages of CD4+ T cells and CD8+ T cells in their peripheral blood.[68]

Immunosuppression in kidney cancer does not always involve decreased levels of T cells. In many cases, T cells are present in large numbers in the TME but demonstrate severely decreased anti-tumor efficacy. Tumor cells can suppress tumor-specific T cells by several mechanisms including (i) blocking T cell recognition of tumor antigens (ii) decreasing T cell effector function and (iii) inhibiting T cell localization to the tumor site. Immune suppression that promotes tumorigenesis can also come from extrinsic factors such as genetic mutations [e.g. severe combined immunodeficiency (SCID)], treatments to prevent transplant rejection, infections (e.g. HIV), or exposure to certain chemicals such as TCE.

Advanced kidney cancer is currently being effectively treated with drugs known as immune checkpoint inhibitors, e.g. anti-PD-1 and/or anti-CTLA-4 antibodies. These antibody treatments block the ability of

tumor cells to suppress T cell activity. These immunotherapies decrease kidney cancer progression, proving that functional T cells are needed to fight kidney cancer.

In the absence of checkpoint inhibitor treatments, kidney cancer progression is associated with increased percentages of terminally exhausted CD8+ T cells in the TME. [69] These ineffective T cells express PD-1 which makes them susceptible to the inhibitory effects of PD-1L-expressing kidney cancer cells. Hence the efficacy of the anti-PD-1 antibody therapies. The functionally ineffectiveness of CD8+ T cells in the TME may be tied in part to their inability to secrete significant IFN–γ in response to tumor antigen stimulation. [35] IFN-γ is cytokine that is primarily secreted by CD4+ T cells and CD8+ T cells. Aside from its role in promoting proliferation and differentiation of immune cells IFN-γ has many anti-tumor effects. It can (a) act a cytotoxic cytokine that initiate tumor cell death, (b) increase the ability of macrophages and dendritic cells to activate anti-tumor T cells, and (c) inhibit the angiogenesis needed for tumor growth. [70] [71] [72] On the other hand, the expression of IFN-γ early in tumorigenesis can promote tumor growth. [70]

Reconciling the pro- and anti-tumorigenic effects of IFN-γ is of great interest since the cytokine seems to serve as a nexus for responsiveness cancer immunotherapy. The different tumorigenic effects of IFN-g may depend on concentration, stage of cancer progression, and the presence of cells and/or other soluble mediators that counteract or enhance the effects of IFN-γ. In any case, IFN-γ is a major player in cancer regulation.

Peripheral blood cells from patients with kidney cancer have fewer IFN-γ–producing cells than healthy controls.[34] Although treatment with IFN-γ alone has not been found to be an effective treatment for kidney cancer, IFN-γ has been shown to contribute to the efficacy of checkpoint inhibitors [70], and the clinical outcomes associated with nonmyeloablative stem cell transplantation in the treatment of kidney cancer. [73]

As described in Opinion 2 extrinsic factors such as TCE that inhibit the number or activity of CD4+ T cells and/or CD8+ T cells and/or alter T cell IFN-γ production would be expected to promote development of kidney cancer.

VIII. OPINION 2. TCE CAUSES IMMUNOTOXICITY THAT HAS BEEN LINKED TO KIDNEY CANCER

A. Epidemiological Studies

Table II lists the epidemiological studies that have examined the association between TCE exposure, immunosuppression, and inflammation. They were all cross-sectional studies, some of which compared TCE-exposed workers to unexposed workers, and some of which compared unexposed workers to those that had been diagnosed with TCE-induced hypersensitivity disease. The studies evaluated a variety of immunological endpoints best represented as specific values such as mg/ml of a serum immunoglobulin or percentages of specific cell types. Consequently, the data was not presented as Odds Ratios which is better suited to comparing yes/no disease incidence in two or more populations. In some cases, the endpoints in a published study were presented as bar graphs or as box and whisker plots. This is not unusual for this kind of data but necessitated describing the relative differences between controls and TCE-exposed rather than presenting actual number values.

Table II. Epidemiological studies examining TCE exposure and immunotoxicity

Study	Endpoints	TCE exposure estimates (ppm)			Other
		Controls <0.03	<12 (mean=5.2)	>12 (mean=38.4)	
Lan *et al*. [74]	Total T cells CD4+ T cells CD8+ T cells B cells NK cells	**Per ml blood** 1356±374 675±200 544±216 227±133 467±279	**Per ml blood** 1310±391 664±220 508±175 194±99 370±148	**Per ml blood** **1124±346 (p=0.0001)** **577±192 (p =0.004)** **430±150 (p=0.007)** **152±68.1 (p=0.001)** **282±145 (p=0.002)**	N=80 Exposed, N=96 Controls Only selected workers from factories that used TCE but had no or negligible levels of other chlorinated solvents
Hosgood *et al*. [75]	Effector memory CD4+T cells Naïve CD4+ T cells Naïve CD8+ T cells	**Per ml blood** 225±93 283±126 216±117	**Per ml blood** **183±55 (p=0.014)** 293±142 212±101	**Per ml blood** **184±89 (p=0.001)** **236±113 (p=0.017)** **152±93 (p=0.0001)**	Same cohort as Lan *et al*, 2013
Lee *et al*. [76]	Serum IgG Serum IgM Effector memory CD4+T cells	**µg/ml** 10.99±2.97 1.18±0.820. 10^3 cells/ml blood 224.9 + 92.9	**µg/ml** **9.24±1.66 (p=0.008)** **0.76±0.34 (p=0.0008)** 10^3 cells/ml blood **181.8 + 56.7 (p=0.042)**	**µg/ml** **8.9±2.15 (p=0.002)** **0.71±0.37 (p=0.002)** 10^3 cells/ml blood 184.5 + 86.1	Same cohort as Lan *et al*,
Zhang *et al*. [77]	Serum IgG Serum IgM	N/A N/A	**Decreased** **Decreased**	**Decreased** **Decreased**	Box and whisker plots; no values, but indication of statistical significance
		Controls	**TCE-induced disease**		
Li *et al*. [78] Compared patients with TCE-induced hypersensitivity to controls with no disease or exposure	Neutrophils Eosinophils Basophils	**10^9/L** 3.53±1.08 1.1±1.7 0.18±0.21	**10^9/L** **7.75±6.8 (p=0.021)** **0.14±0.19 (p=0.013)** **0.02±0.01 (p=0.002)**		**Saw clearly doubled increase in TNF-a - producing CD4+ T cells: just bar graphs, no values.**
Kamijima *et al*. [79] Compared patients with TCE-induced hypersensitivity to controls	**S**erum levels of TNF-α	% more than 3 SD above mean control values 4%	% more than 3 SD above mean control values **79% (p=0.01)**		N=28 with disease, N=48 Controls Measured end of shift TCA levels, but no estimates for TCE
	Serum levels of: IL-1β				**Significantly increased serum levels of all three cytokine shown as**

Jia et al. [80]	TNF-α IL-6			**bar graphs and dot plots**

Bolded values are significantly different from controls. P-values were provided for these values.

The epidemiological studies described how TCE exposure generated immune suppression as indicated by (a) decreased serum levels of IgG and IgM, and (b) decreased blood levels of lymphoid populations including CD4+ T cells, CD8+ T cells, B cells and NK cells. Although this report is focused on adult exposure it is interesting to note that *in utero* exposure to TCE in contaminated well water statistically increased the childhood incidence of leukemia, kidney/urinary tract infections and lung/respiratory infections.[81] Aside from markers of immune suppression, indications of inflammation such as significantly increased levels of TNF-α, IL-1β and IL-6 were found in workers exposed to TCE.

The epidemiological studies shown in Table II focused on endpoints of TCE-induced immune suppression. However, aside from its ability to cause hypoactivity of the adaptive immune response TCE can in some cases cause hyperactivity of the adaptive immune response. As myself and others have shown TCE exposure can promote hypersensitivity and increased T cell and B cell function in humans and animal models.[18, 20, 82-86] These studies provide additional evidence of TCE-induced immune dysfunction.

B. Animal studies

Even though there are some differences, mice and humans share many components of the immune system, and mouse models have enabled breakthroughs in our understanding of the human immune system. Consequently, the results obtained from TCE-exposed mice are expected to be relevant to human exposure. Inhalation exposure to TCE in mice enhanced susceptibility to pulmonary infection, an appropriate endpoint for immune suppression.[87] Similarly, mice exposed to TCE in drinking water showed significantly decreased cell-mediated immunity and bone marrow stem cell colonization.[88] High-dose exposure to TCE for 4 weeks caused a 70% decrease in antigen-induced antibody production in Sprague-Dawley rats.[89]

Although TCE can cause immunosuppression in animal models, it can also cause inflammation. Mice sensitized to dermal TCE exposure showed dramatic increases in the levels of IL-6, IL-1β and TNF-α in the kidney. [90] The functional significance of these TCE-induced inflammatory mediators was evident when a TNF-α inhibitor was shown to relieve liver damage in TCE exposed mice.[91]

Like the findings in humans, studies in animal models have shown that TCE can alter the number, function and/or phenotype of lymphoid cell population in blood, spleen and thymus. [84, 88, 89]

As mentioned above the cytokine IFN-γ has an outsized role in determining tumor progression and regression.[70] We have shown that TCE exposure in mice alters IFN-γ production at the level of protein production, gene expression and epigenetic alterations.[13, 14, 16] TCE-induced alterations in IFN-γ production represent another mechanism by which TCE can promote carcinogenicity.

C. Mechanism of Action

The function of immune cells, similar to almost all cells, is largely mediated via gene expression. We and others have shown that TCE-induced changes in IFN-γ levels reflect a corresponding change in expression

of *ifng*. [16, 92] We have linked the TCE-induced change in gene expression to at least two mechanisms: (a) binding to T cell proteins in a way that triggers transcription factor activation and downstream gene expression, and (b) inducing long-term epigenetic alterations that help control gene expression.[10, 12 13 4, 14, 15] Both of these TCE mechanisms have subsequently been confirmed in humans. [78, 93, 94, 95]

The fact that TCE generates epigenetic alterations in both humans and animal models provides a mechanism to explain why TCE effects can remain even after exposure cessation.[5] Along these lines occupational TCE exposure was found to increase aging in terms of epigenetic alterations in lymphocytes by two years compared to chronological aging [96]

D. Federal and International Agency Conclusions

USEPA Risk Evaluation of Trichloroethylene (2020): "Overall, immunotoxicity in the form of both autoimmunity and immunosuppression following TCE exposure are supported by the weight of evidence." The regulatory values derived from a mouse study of immunosuppression [87] were used by the EPA to evaluate the potential risk to workers by TCE exposure**.** [2]

E. Summary

TCE has been shown to alter several immune parameters in humans and animal models that are also seen in idiopathic kidney cancer. These alterations are clear indications of immunotoxicity. There are studies in animal models that confirm TCE-induced immunosuppression, and potential mechanisms have been described that provide biological plausibility. Since both immunosuppression and inflammation are crucial mediators of kidney cancer, TCE-induced immunotoxicity that encompasses both processes is likely to promote the etiology of this disease.

IX. OPINION 3. TCE INDUCES OXIDATIVE STRESS WHICH HAS BEEN LINKED TO KIDNEY CANCER

A. Background

In addition to inducing immune system changes linked to tumorigenesis, TCE also increases oxidative stress which promotes tumor development.

Oxidative stress is considered the cellular imbalance between antioxidants and oxidants [reactive oxygen species (ROS)]. ROS are a byproduct of mitochondrial respiration during normal cell function and can serve as important signaling molecules in normal physiology. Cells have a protective system mediated by antioxidants designed to keep ROS at physiologically normal levels. However, an imbalance between the formation and destruction of ROS often leads to excess intracellular accumulation of ROS, a condition known as oxidative stress.

The excess ROS associated with oxidative stress causes cell damage through harmful reactions with proteins, lipids and DNA. It is therefore not surprising that oxidative stress is a causative factor for multiple diseases.[97] This is at least in part due to its ability to promote chronic inflammation. [97, 98]

Although the role of oxidative stress in later stages of tumorigenesis is complicated, its ability to augment inflammation during initial stages of cancer development gives it a clearcut role in early

tumorigenesis. Oxidative stress has been implicated as an intermediate in DCVC-induced DNA damage following TCE exposure. [99]Aside from promoting cell transformation, reactive oxygen species have been shown to promote tumor development by suppressing tumor-specific T cells.[100]

ROS in the tumor microenvironment can be derived from the tumor cells and/or from cells of the innate immune system such as macrophages which are recruited to the tumor site.

B. TCE-induced oxidative stress

A dose-dependent association between TCE exposure and systemic markers of oxidative stress has been reported in a mouse model.[101]

The functional relationship between TCE-induced toxicity and TCE-induced oxidative stress has been especially well-studied in a mouse model of autoimmune disease. In that model, indicators of oxidative stress in TCE-exposed mice include increased levels of lipid peroxidation-derived aldehydes such as malondialdehyde, and higher serum iNOS and nitrotyrosine.[102] It is still not clear how TCE increases oxidative stress. However, signs of oxidative stress have been found in liver[103], placenta[104], gut[105], embryonic heart[106], and kidney [107] following TCE exposure. TCE-induced oxidative stress is associated with kidney damage [107], skin hypersensitivity [108], functional neurotoxicity [109], autoimmune disease[110], and liver cancer.[111] DCVC, the kidney metabolite of TCE, has been shown to generate oxidative stress-induced cell death on its own.[112]

Oxidative stress is not just a by-product of TCE exposure; it appears to be important in mediating TCE toxicity. This has been demonstrated by showing that anti-oxidant treatments protect against cardiac toxicity, dermal hypersensitivity and autoimmunity caused by TCE exposure. [110, 113, 114] Making the same point was the finding that the absence of anti-oxidant activity exacerbates TCE-induced neurotoxicity.[115] DNA damage mediated by TCE-induced oxidative stress also appears to be one mechanism for TCE genotoxicity in liver cells.[80]

C. Summary

Oxidative stress, together with chronic inflammation, are important components in the development of several types of cancer, including kidney cancer. TCE increases oxidative stress in many organ systems, including the kidney, in humans and mouse models. *Thus, it is more likely than not that TCE-induced oxidative stress represents another mechanism by which the chemical, together with TCE- induced genotoxicity, inflammation, and T cells inhibition, work together to cause kidney cancer.* A model of this *multi-component mechanism* for TCE-induced kidney cancer is illustrated in Figure 2.

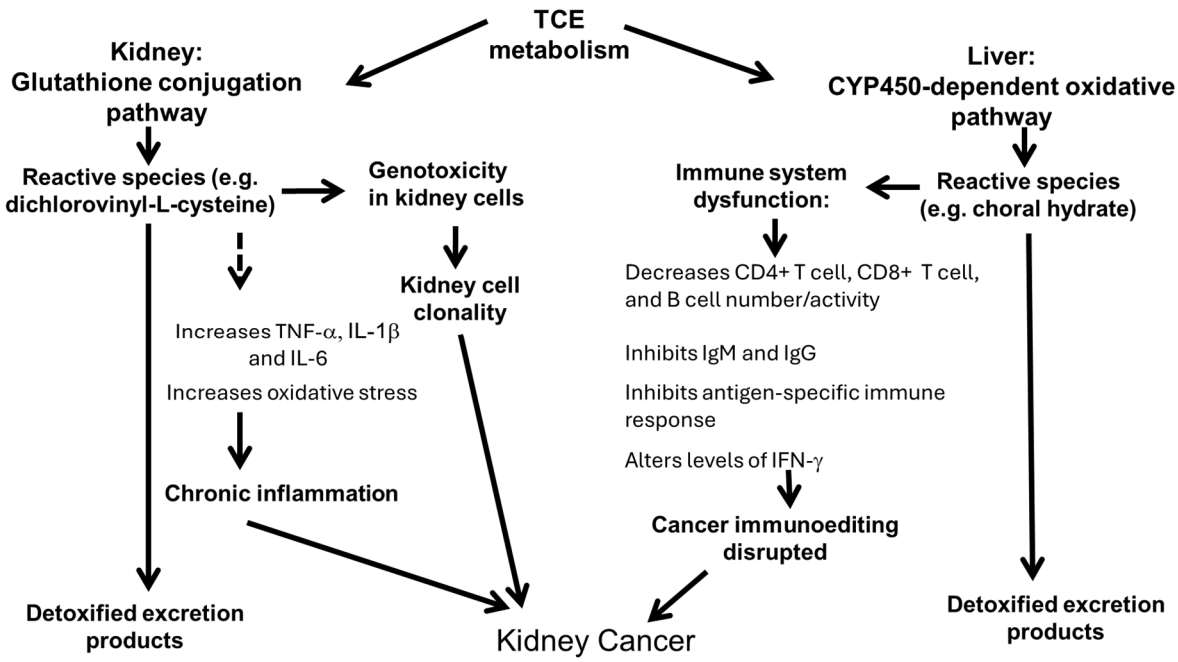


Figure 2. Model of how TCE promotes kidney cancer

X. OPINION 4. TCE LEVELS AT CAMP LEJEUNE WERE HAZARDOUS TO HUMAN HEALTH AND ARE KNOWN TO CAUSE KIDNEY CANCER

When assessing the likelihood that a toxicant causes pathology, environmental levels, duration, temporality and concentration are usually considered. These will be addressed here regarding the Camp Lejeune plaintiffs.

A. TCE levels at Camp Lejeune

The ATSDR reconstructed the VOC concentrations in the drinking water at Camp Lejeune.[116] The agency reported the levels of TCE at the Hadnot Point water treatment plant reached an estimated maximum average of 783 μg/L, compared to a maximum measured value of 1,400 μg/L, during the time period between August 1953 and December 1984. The Holcomb Boulevard water-distribution contained estimated maximum concentrations of TCE of 32 μg/L prior to 1972, and an estimated maximum concentration of 66 μg/L between 1972 and 1985. Levels of PCE at the Tarawa Terrace water treatment plant reached an estimated maximum level of 215 μg/L, and a maximum monthly average level of 183 μg/L, and exceeded the EPA MCL (5 μg/L) from November 1957 and February 1987. These levels of TCE and PCE in the drinking water were hazardous to human health and are known to cause kidney cancer.

I have also reviewed the ATSDR water modeling reports that are publicly available and the summary tables of Plaintiff's expert Morris Maslia. These levels shown to be present at Camp Lejeune are hazardous to humans generally and are known to cause kidney cancer.

B. TCE exposure duration

As mentioned earlier, the ATSDR did a comprehensive examination of mortality causes in Marines and non-service personnel stationed at Camp Lejeune during the years between 1975-1985. [27, 40, 41] The ATSDR found sufficient evidence that TCE caused kidney cancer. The Marines in the mortality studies served an average of 18 months on the base. The non-military personnel worked at the base for an average of 29 months. These studies, which showed increased rates of kidney cancer, provide strong evidence that these amounts on time on base were sufficient to cause kidney cancer.

Although the ATSDR did not study the exposure duration required to cause disease, they did say that epidemiological data did not contradict a minimum duration of 30 days. [27] They went on to say; "Moreover the results from the Camp Lejeune mortality studies suggest that a 30 day minimum duration requirement may be appropriate since the elevated risks for some of the diseases evaluated were observed for exposure durations of 1-3 month."

A recent new evaluation of the Camp Lejeune data similarly concluded that based on the concentrations of contaminants at the base just one month exposure was sufficient to increase the likelihood of developing cancer.[117] This is consistent with my many years of experience with TCE and the research I have conducted and literature I have reviewed.

All of the plaintiffs in this case were exposed to the contaminants at Camp Lejeune for longer than one month.

C. TCE Disease latency

When discussing the limitations of the ATSDR's 2024 examination of cancer incidence among Camp Lejeune personnel, Bove noted that the median age of personnel at the end of the follow-up examination was 57 years.[42] Bove went on to note that the cancers that have been associated with occupational TCE exposure such as NHL, and cancers of the kidney and liver, the median ages at diagnosis are 67, 64 and 65 years respectively. Thus, it is likely that the cancer incidence of the people exposed to TCE at Camp Lejeune would have increased if the follow-up had been extended.

A long lag time between chemical exposure and cancer diagnosis is not unusual. A meta-analysis of three Nordic cohort studies examined risk of cancer following 5.5 – 6.3 years of occupational TCE exposure. Even after a lag period of 20 years, TCE exposure increased the risk of liver cancer (SIR 2.09; 95% CI 1.34-3.11).[118]

D. TCE exposure level

There is no one methodology that clearly defines the true minimum concentration of TCE that causes kidney cancer. However, a combined WOE approach can nevertheless demonstrate levels that have been shown to be hazardous to human beings generally and are known to cause kidney cancer.

The epidemiological studies in Table I provide evidence that TCE and other VOC cause kidney cancer under the conditions found at Camp Lejeune. However, using these studies to define the true minimum dose or true minimum duration to cause kidney cancer is challenging. Dose-duration studies conducted

to assess hazards are confined to drug clinical trials. It would be unethical to conduct similar studies using known toxicants. Some of the epidemiological studies in Table I compared results from TCE-exposed to non-TCE exposed without attempting to define exposure levels. Some devised relative exposure classifications (e.g. low, medium, high) without defining specific concentrations. However, there were epidemiological studies that did describe specific exposure levels and found an increased hazard for kidney cancer has been associated with levels of PCE as low as 1-155 μg/L-months, or levels of total VOC at Camp Lejeune as low as 1-4,600 μg/L-months.[40] Other studies showed increased kidney cancers following TCE exposure of 0-25.4 μg/L for 5 years[38], or less than 76 ppb.[49] These studies demonstrate that the levels of TCE at Camp Lejeune were hazardous to human health and known to cause kidney cancer.

Using epidemiological studies to define a hazard threshold underestimates the lowest numbers hazardous to human beings and that cause kidney cancer because it is probable that there is risk at levels below those estimated in an epidemiological study. Epidemiology, however, is generally considered to be the best evidence of these exposure levels being hazardous to humans generally and known to cause kidney cancer. If these studies exist they should be utilized first in this analysis, as I have done in this report.

A second potential way to discuss the relationship between exposure levels and increased cancer incidence involves the use of regulatory values such as the oral slope factor. While not directly related to causality, such data points can be referenced in an overall evaluation of the likelihood that a particular exposure caused a disease outcome. Regulatory values are derived by the EPA based on cumulative dose-response data from epidemiological and animal studies. They are designed to estimate future risk from a chemical in order to inform mitigation decisions. Of course, using estimates of future risk does not fit an analysis for determining causation for individuals who already have cancer because the risk of someone who has cancer getting cancer is of course 100%. However, when kept in the proper context, these values can be referenced to discuss whether a known chemical exposure could be expected to increase the incidence of cancer.

Predictions based on oral slope factors probably underestimate cancer risk since real accuracy would require defining the full level of exposure (e.g. involving multiple routes of exposure) and the additive effects of co-exposure to other chemicals with their own slope factors. However, even if we did not have the data clearly showing an increase in kidney cancer incidence at Camp Lejeune, the oral slope factor would predict such an increase. Thus, considering both methodologies, and understanding the limitations of the oral slope factor and risk assessment in this situation, it is reasonable to focus on the epidemiological data first and then consider whether a risk assessment analysis is consistent.

There have been several attempts to use cancer slope factors generally to assess the drinking water at Camp Lejeune. The ATSDR in its public health assessment in 2017 looked at risk assessments generally when conducting its analysis. The ATSDR data in this regard confirms that the levels of the toxins in the water at Camp Lejeune are hazardous to humans generally and based on the oral slope factors would be expected to increase cancer incidence.

Second, the oral cancer slope factor is expressed in mg/kg/day and is used to predict additional cases of cancer per million people exposed to a particular concentration of a chemical for a lifetime. The TCE oral slope factor specific for kidney cancer is 5×10^{-2} mg/kg/day. Active military personnel are estimated to ingest from 4 to 10 L/day depending on temperature and activity level and to weigh a default 80 kg.

https://www.epa. gov/sites/default/files/2015-11/documents/OSWER-Directive-9200-1-120-ExposureFactors.pdf. As mentioned in Opinion 5 amounts of TCE ingested from drinking water need to be at least doubled to factor in dermal and inhalation exposure routes to calculate total exposure.

To estimate the increased cancer risk from chemical exposure, the oral cancer slope factor for a specific chemical is multiplied by the lifetime exposure (in mg/kg/day). An example of its use will be provided here using TCE levels of 783 μg/L which represent the maximum monthly average of TCE found in the drinking water at Hadnot Point.[116] Using default values of 4- 10 L/day of water a Marine's exposure to TCE would be between 0.078 mg/kg/day (0.783 mg/L x 2 (accounting for dermal and inhalation x 4 liters/day/80 kg) to 0.196 mg/kg/day (0.783 mg/L x 2 (accounting for dermal and inhalation x 10 liters/day/80 kg). If you multiply that by the oral slope factor for TCE (0.05 per mg/kg/day) you would predict at least between 3,900 and 9,800 extra cancers per million people for individuals chronically exposed to that level of TCE. A more accurate analysis would need to adjust for the duration of exposure and use a more specific estimate of the contribution from dermal and inhalation exposure. In addition, these values are for TCE alone and do not take into account coexposure effects from the other contaminants. These values are also limited to adult exposure. According to the ATSDR children between the ages of 0-3 years old who lived on the base for 3 years were predicted to experience at least 4,500 extra cancers per million people from the cumulative chemical exposure.
https://stacks.cdc.gov/view/cdc/43951

A third way to get perspective on TCE exposure levels and pathology involves the new Existing Chemical Exposure Limit (ECEL) for TCE proposed by the EPA on October 31, 2023. The ECEL was published in the Federal Register as a proposed rule concerning *Trichloroethylene: Regulation Under the Toxic Substances Control Act* https://www.govinfo.gov/content/pkg/FR-2023-10-31/pdf/2023-23010.pdf The EPA is proposing a new ECEL for TCE of either 4.0 ppb or 1.1 ppb for occupational inhalation exposures as an 8-hour time-weighted average (TWA). Only exposures equal to or below the ECELs are considered free from an unreasonable risk for chronic cancer and non-cancer and acute non-cancer inhalation endpoints.

The proposed 1.1 ppb (0.0059 mg/m^3) ECEL is approximately 100,000 times lower than the OSHA PEL of 100 ppm for an 8-hour TWA. This reflects the EPA's commitment to using recent advances in modeling and scientific interpretation of toxicological data to devise new regulatory guidelines environmental hazards.

Using the default air intake values (15.2 m^3/day for adult males) provided by the ATSDR[1] it is possible to estimate TCE exposure based on the ECEL of 0.00037 mg/kg/day for an 8-hour day. [15.2 m^3/day divided by 24 hours = 0.63 m^3 air intake per hour; 0.63 m^3 air/hour x 0.0059 mg/m^3 = 0.0037 mg/hour x 8 hours/80 kg = **0.00037 mg/kg/day**]. In contrast, a marine's exposure to 783 μg/L TCE in Camp Lejeune drinking water with a 4 L ingestion rate/80 kg = **0.039 mg/kg/day**. Thus, even with a conservative drinking water rate of 4 L/day, the Marine at Camp Lejeune would have been exposed on a daily basis to a level of TCE almost 100-times higher than the level thought not to be unsafe. This level of TCE exposure would need to be adjusted upward to reflect inhalation and dermal exposure.

[1] *See* https://www.atsdr.cdc.gov/hac/phamanual/appg.html.

It can be reasonably concluded that the levels of TCE at Camp Lejeune were sufficient to threaten the health of Marines and civilians on the base and were a special threat to children living on the base.

E. Summary

Taking into account disease latency, exposure levels and exposure duration, it is more likely than not the TCE exposure at Camp Lejeune was sufficient to promote the development of kidney cancer and was hazardous to humans.

XI. OPINION 5. TCE-INDUCED KIDNEY CANCER IN THE PLAINTIFFS WAS AUGMENTED BY AGGREGATE EXPOSURE VIA INHALATION AND DERMAL ROUTES, AND BY CUMULATIVE CO-EXPOSURE TO OTHER CONTAMINANTS IN THE DRINKING WATER

There is considerable evidence that the toxic response to a chemical such as TCE by one route of exposure can be augmented by exposure to the same chemical by a different route of exposure or by co-exposure to another chemical. This is an important consideration since cumulative and aggregate exposure assessments more realistically depict real-world exposures in both occupational and environmental settings. This is certainly true at Camp Lejeune. Aggregate exposure assessments are used when an individual is exposed to a single contaminant via different routes. Cumulative exposure assessments consider the hazards posed by multiple toxicants.

A. Aggregate exposure to TCE

On April 18, 2024, Michal Freedhoff, the EPA Assistant Administrator for the Office of Chemical Safety and Pollution Prevention, signed the following document: *Action: Final Rule Title: Procedures for Chemical Risk Evaluation Under the Toxic Substances Control Act (TSCA).* https://www.epa.gov/system/files/documents/2024-04/prepubcopy_frl-8529-02-ocspp_fr_doc_aa_esignature_verified.pdf. *In this document the EPA noted that the inclusion of all exposure pathways relevant to the chemical substance should be taken into account when assessing its effects on human health.* TSCA is designed to assess the hazards posed by occupational and consumer exposures. However, the principle also holds true for human environmental exposure.

At Camp Lejeune hazard assessment has focused on TCE exposure from ingesting contaminated drinking water. However, when estimating the hazards posed by TCE it is important to also consider inhalation and dermal exposure resulting from the use of the TCE-containing drinking water for cleaning and bathing. Results from PBPK modeling and from human experimental samples have shown that inhalation and dermal exposure from TCE-contaminated water is at least equal to that from ingestion. [119, 120] A 2024 study by Rosenfeld *et al.* used new methodology to quantify cancer risk for the Marines who had lived at Camp Lejeune between 1953 and 1986.[117] They estimated that most of the increased cancer risk (59%) was in fact due to inhalation from the contaminated drinking water, while ingestion and dermal exposure contributed 34% and 5.5% respectively. They concluded that the inhalation exposure pathway posed about 1.7 times greater risk than the ingestion pathway. This suggests that, at the very least, one should double the ingestion exposure of TCE to estimate total TCE exposure at Camp Lejeune.

Breathing indoor air contaminants in Camp Lejeune's buildings due to vapor intrusion is another potential pathway of exposure. Volatile chemicals such as TCE in contaminated shallow groundwater can

evaporate and move upward through the ground surface into indoor air of overlying or nearby buildings—this process is called vapor intrusion. At this time ATSDR is evaluating about 150 buildings at Camp Lejeune. https://www.atsdr.cdc.gov/ sites/lejeune/Vapor-Intrusion-PHA.html. The results are expected in the fall of 2024. Although the values obtained will reflect current rather than historical levels of TCE in the groundwater, they may at least provide some insight into the contribution of this exposure pathway to total exposure.

B. Cumulative co-exposure to TCE and other contaminants

It is widely acknowledged that many instances of environmental contamination involve concurrent exposures to a mixture of compounds that may induce similar effects over exposure periods ranging from short-term to lifetime. This is certainly the case at Camp Lejeune.

The assessment of chemical mixtures is an area of active scientific investigation. The ATSDR is committed to better defining the impacts of chemical mixtures.[2] To carry out this legislative mandate, the ATSDR's Division of Toxicology has developed and coordinated a mixtures program that includes *in vivo* and *in vitro* toxicological testing of mixtures, quantitative modeling of joint action, and methodological development for assessment of joint toxicity.[3] The ATSDR has identified 16 Final or Draft Interaction Profiles describing chemical mixtures of human health concerns. Four of the Interaction Profiles contain TCE. One of these four mixtures contains TCE and PCE, and the other contains TCE and vinyl chloride.

The EPA is similarly committed to studying mixtures as a means to inform risk assessment. The EPA's *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures* was designed to generate a consistent Agency approach for evaluating data on the chronic and subchronic effects of chemical mixtures. It is a procedural guide that emphasizes broad underlying principles of the various science disciplines (toxicology, pharmacology, statistics) necessary for assessing health risk from chemical mixture exposure. https://assessments.epa.gov/risk/document/&deid=20533. The EPA defines mixtures as any combination of two or more chemical substances regardless of source. In some instances, complex mixtures consist of multiple compounds that are generated simultaneously as byproducts from a single chemical such as degradation of PCE or TCE. Mixtures can also consist of unrelated chemicals which because of inadequate but proximal disposal processes end up contaminating the same water supply. Both of those definitions apply to the contamination at Camp Lejeune.

The chemicals in a mixture can interact in a manner that is additive or greater than additive (e.g. synergistic). The term additive describes the situation when the combined effects of two or more chemicals equal the sum of the effects of the chemicals acting independently. Response addition has often been used for the risk assessment of mixtures of carcinogens.[121]

Because of the complexity of considerations that must be undertaken to develop a chemical mixtures health risk assessment, the EPA notes that it is not practical to recommend a clear listing of default procedures that covers all cases. The Agency describes different approaches to a quantitative health risk assessment of a chemical mixture, all of which are outside the scope of this report. However, general considerations for mixtures assessment, such as functional and chemical similarities and similar

[2] *See* https://www.atsdr.cdc.gov/mixtures/assessment.html.
[3] *See* https://www.atsdr. cdc.gov/interactionprofiles/ip02.html

toxicodynamics, make it likely that co-exposure to the contaminants at Camp Lejeune induced additive toxicity and carcinogenicity.

In terms of structural similarity TCE, PCE, and vinyl chloride all contain 2 carbon molecules with three, four, or one chloride molecules respectively (**Figure 3**).

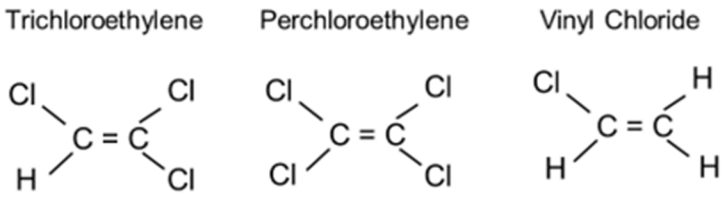


Figure 3. Structure of TCE, PCE and vinyl chloride

There are also several functional similarities among TCE, PCE, benzene, and vinyl chloride. They have qualitatively similar metabolic pathways in both rodents and humans.[122] This includes oxidative metabolism in the liver and conjugative metabolism in the kidney, although there are some quantitative differences in the metabolites formed. Oxidative metabolism of TCE, PCE, vinyl chloride, and benzene is largely, but not solely dependent on the same enzyme, CYP2E1.[123] All four chemicals are converted into toxic and reactive metabolites that have been linked to cancer in epidemiological studies, including kidney cancers. [40, 41, 124]

Taken together, it is more likely than not that exposure to three known carcinogens (TCE, benzene, and vinyl chloride) and one likely carcinogen (PCE) would have an additive effect on tumorigenicity. Rosenfeld *et al.* examined the combined cancer risk from co-exposure to the different contaminants in the drinking water at Camp Lejeune. [117] They predicted that the cancer risk from TCE exposure would be increased by co-exposure to other contaminants at Camp Lejeune. The study of TCE co-exposure effects is still relatively new. However, I, as well as others, have demonstrated that co-exposure to other chemical stressors can augment TCE-induced toxicity and gene expression.[21, 125, 126] Although these studies did not examine TCE in combination with PCE, benzene, or vinyl chloride, they provide proof of concept that co-exposure effects should be considered when assessing the hazards such as kidney cancer posed by TCE exposure.

C. Overall Summary for Opinion 5

Estimating kidney cancer risk for the Marines at Camp Lejeune should also take into account inhalation and dermal exposure from the contaminated drinking water, and perhaps inhalation of indoor air contaminated by vapor intrusion. It should also consider the likely additive effects of co-exposure to three other known and/or likely carcinogens vinyl chloride, benzene and PCE.

Signature. I hold all of the above opinions to a reasonable degree of scientific certainty. I reserve the right to supplement and/or review my opinions as presented in this report as new information becomes available.

12-8-24

Kathleen M. Gilbert, PhD Date

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Appendix A

KATHLEEN M. GILBERT, PHD
IMMUNOTOXICOLOGIST

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800 Shire Court, Fort Collins, CO 80526

SUMMARY: Although initially trained as a molecular immunologist with an emphasis on immune tolerance and autoimmune disease, Dr Gilbert has for the last 25 years focused her research on the immunotoxicity of trichloroethylene (TCE). She has authored over 30 articles examining the immunotoxicity of TCE or related products, and co-edited a book entitled *Trichloroethylene: Toxicity and Health Risks*, Springer, New York/Heidelberg. She is a member of the US EPA's Scientific Advisory Committee on Chemicals (SACC) which has thus far reviewed risk evaluations for ten high-priority chemicals, including TCE, that were identified as part of the Toxic Substances Control Act. Dr. Gilbert has provided risk assessments for human exposure to TCE and other chemicals including perchloroethylene, vinyl chloride, and benzene. Dr. Gilbert is a long-standing member of the Society of Toxicology.

EDUCATION:

Occidental College, Los Angeles, CA, BS, Biology, 1976
Tulane University, New Orleans, LA, PhD, Immunology, 1980

PROFESSIONAL EXPERIENCE:

Postdoctoral Research Associate: Sloan Kettering Institute, New York, NY
1980 -1982
Research Associate, Sloan-Kettering Institute, New York, NY
1982 -1985
Visiting Worker: National Institute for Medical Research, London, UK
1985 -1987
Senior Research Associate: Department of Immunology, The Scripps Research Institute, La Jolla, CA,1987 -1991
Assistant Member (Assistant Professor): The Scripps Research Institute, La Jolla, CA
1991 -1994
Assistant Professor: Department of Microbiology and Immunology, University of Arkansas for Medical Sciences, Little Rock, AR
1995 – 2001
Associate Professor: Department of Microbiology and Immunology, University of Arkansas for Medical Sciences, Little Rock, AR
2001 – 2010
Professor (tenured), Department of Microbiology and Immunology, University of Arkansas for Medical Sciences, Little Rock, AR
2010- 2017 (Retired)

Secondary Appointments at UAMS: Dept. of Pediatrics, 2002-2017

Dept. of Pharm. and Toxicology, 2010-2017

Adjunct Professor, Dept. of Microbiology, Immunology, and Pathology, Colorado State University, Fort Collins, CO, 2017-Present

TEACHING/MENTORING

Teaching Medical Students at UAMS

Course	Total Hours	Level	Years
Medical Microbiology-Immunology-Parasitology Now called *Disease and Defense*	Three-five 1-hour lectures/year Three 3-hour Patient-Oriented Problem Solving sessions/year	2nd year 1st year	1995 – 2011 2011- present

Teaching Graduate Students at UAMS

Course	Total Hours	Level	Years
Immunology	six 1.5-hour lectures/year	1st year	Course Director, 1995 - 2002 Lecturer, 1995 - 2017
Advanced Immunology	three 2-hour lectures/year	2nd-3rd year	1995 -1997
Molecular Mechanisms of Immunology	four 2-hour lectures/year	2nd-3rd year	1998 - 2017
Current Topics in Immunology	two 1-hour lectures/year	1st-5th year	1995 - 2017
Biochemical Methods	two 1.5-hour lectures/year	1st-2nd year	2000 - 2002
Methods in Pharmaceutical Sciences	one 1.5-hour lecture/year	1st-2nd year	2001
Molecular & Translational Toxicology	three 1.5-hour lectures/year	2nd -3rd year	2002 - 2017
Systems Toxicology	three 1.5-hour lectures/year	2nd and 3rd year	2009 - 2017

MENTORING

Dr Gilbert has served as a dissertation/thesis committee chair or member for 22 graduate students at UAMS. She has served as mentoring committee chair or member for 8 junior faculty members at UAMS, and has mentored 21 other undergraduates, graduate students and faculty members as part of INBRE grants or Honors in Research Programs.

RESEARCH/SCHOLARLY WORK

Most Recent Research Support

Title	Funding Agency	Dates	Direct Costs	Role	Effort
Extramural					
Developmental Programming of TCE-induced autoimmune disease R01ES021484	NIEHS	12/1/12 – 11/30/17	$1,372,000	Co-Principal Investigator	30%
Gender Supplement to R01ES021484	NIEHS	9/15/14-10/31/16	$99,724	Co-Principal Investigator	0%
Determining how trichloroethylene alters $CD4^+$ T cell function: 1R01ES017286	NIEHS	1/07/10 - 12/31/14	$675,000	Principal Investigator	40%
Trichloroethylene toxicity and remediation	Competitive grant funded by Organic Compounds Property Contamination class action settlement (CV 1992-002603)	7/01/08-6/30/15	$735,000	Principal Investigator	25%
Training program in the pathophysiology of renal disease: 5T32DK061921 (PI: Portilla)	NIDDK	2006-2011	$603,335	Faculty Mentor	0%
Intramural					
Developing an Immunotoxicology Center in Arkansas	Arkansas Biosciences Institute	7/01/02 – 6/30/17	$1,500,000	Principal Investigator	10%

Past Research Support

Title	Funding Agency	Dates	Direct Costs	Role	Effort
Extramural					

Screening disinfection by-products for their ability to promote autoimmunity	Environmental Protection Agency	10/01/01 -9/31/04	$500,000	Principal Investigator	25%
Mechanisms of chlorinated ethylene-induced autoimmunity, Proposal No. R826409	Environmental Protection Agency	3/25/98 - 3/24/01	$278,356	Principal Investigator	25%
Cyclin-dependent kinase inhibitors mediate T cell anergy: MCB-9817191	National Science Foundation	3/15/99 - 3/14/02	$230,660	Principal Investigator	25%
The use of G1 blockers in a novel system of immune intervention	National Arthritis Foundation	1/1/02 – 12/21/04	$270,000	Principal Investigator	25%
Use of tributyrin as a novel system of immune intervention, Proposal No. KG071598	Arthritis Foundation, Arkansas Chapter	7/15/98 - 10/15/99	$31,280	Principal Investigator	25%
Mechanism of Toxicant-induced T cell Suppression; Grant No. 187-B	American Cancer Society	2/1/96 - 1/31/97	$15,000	Co-principal investigator	25%
A Novel System of Immune Intervention: Grant No. J246	R.W. Johnson Pharmaceutical Research Institute	10/1/92 - 9/30/94	$129,032	Principal Investigator	35%
Mechanisms of renal tubular epithelial cell injury (PI: S. Shah), PO1-DK-58324	NIDDK	2001-2006		Core Director	5%
Suppressor B cells	Arthritis and Rheumatism Council, UK, Project Grant	1986-1987	$45,000	Principal Investigator	100%
Effect of Th cell Tolerance on Cell Cycle Components: Proposal No. MCB-9308198	National Science Foundation	6/1/93 - 5/31/95	$18,000	Principal Investigator	25%
A Novel System of Immune Intervention: Proposal No. 96-B-37	Arkansas Science and Technology Authority Award	1/31/96 - 1/30/97	$33,050	Principal Investigator	30%
Mechanism of B cell suppression	International Union Against Cancer	1985-1986	$16,000	Principal Investigator	100%
National Research Service Award	USPHS	1980-1983		Postdoctoral Fellow	100%
Comparison of the effects of methyl palmitate and glucan on tumor growth	Cancer Association of Greater New Orleans	1978	$900	Graduate Student	100%

Intramural					
Interventive Therapy for Type I Diabetes	Children's University Medical Group	7/1/05-6/31/07	$39,500	Principal Investigator	10%
Inactivating autoreactive T cells by HDAC inhibitors	Sturgis Charitable Trust	2/01/10 – 9/30/10	$24,970	Principal Investigator	0%

Manuscript review activities

Journal	Year Started
Journal of Immunology	1994
Cellular Immunology	1994
Blood	2000
Toxicology and Applied Pharmacology	2006
American Journal of Transplantation	2007
Biochemical Pharmacology	2007
Endocrine	2009
International Journal of Environmental Sciences	2008
Libertas Academica	2009
Toxicological Sciences	2009
Journal of Environmental Science and Health	2010
International Journal of Nephrology and Renovascular Disease	2010
Transplant Immunology	2008
Toxicology	2011
BMC Pharmacology	2011
ISRN Immunology – Editorial Board	2011
Chemical Research in Toxicology	2012
Toxicology Research	2012
Journal of Immunotoxicology – Ad hoc Editor	2012
Environmental and Molecular Mutagenesis	2013
International Journal of Molecular Sciences – Guest Editor for special issue on "Environmental Toxicants and Autoimmune Disease	2013
Drug Design, Development and Therapy	2015
BMC Medical Genomics	2015
Expert Review of Gastroenterology & Hepatology	2015
Environmental Health Insights	2015
Neurotoxicology	2015
Annals of Neurology	2016
PLOS ONE	2016
Inhalation Toxicology	2016

Grant review activities

Agency	Study Section	Years

National Science Foundation	Signal Transduction and Regulation	1996
National Science Foundation	Biocomplexity	2000
Environmental Protection Agency	Experimental Toxicology	2007
National Institutes of Health	Superfund Basic Research (ZES1 LWJ-M)	2009-2015
National Institutes of Health	Systemic Injury by Environmental Exposure (SIEE)	2016
National Institutes of Health	Digestive, Kidney and Urological Systems (DKUS-A)	2009
National Institutes of Health	Immunology (IMM-E)	2009
National Institutes of Health	Infectious Disease and Microbiology (IDM-C) IFG	2009
Wellcome Trust		2006
RJ Reynolds Foundation	External Research Program	2006 2009
Louisiana Board of Regents		2007
UAMS Medical Research Endowment Grant awards Hornick Grant UAMS Pilot Study Grants UAMS Center for Clinical and Translational Research UAMS Bridging Grants ACHRI Children's University Medical Group awards		1999-2017
National Institutes of Health	Environmental Health Sciences Review Committee for T32 applications	2013

PUBLICATIONS (Peer-reviewed):

- Byrum, S.D., Washam, C.L., Patterson, J.D., Vyas, K.K., **Gilbert, K.M**., and Blossom, S.J. Continuous Developmental and Early Life Trichloroethylene Exposure Promoted DNA Methylation Alterations in Polycomb Protein Binding Sites in Effector/Memory CD4$^+$ T Cells**.** *Frontiers in Immunology* Aug 28;10:2016, 2019.
- Khare, S., Gokulan, K., Williams, K., Bai, S., **Gilbert, K.M.**, and Blossom, S.J., Irreversible effects of trichloroethylene on the gut microbial community and gut-associated immune responses in autoimmune-prone mice, *Journal of Applied Toxicol*ogy 39:209 2019.
- Blossom, S.J**.** and **Gilbert, K.M**. Epigenetic underpinnings of developmental immunotoxicity and autoimmune disease. *Current Opinion in Toxicology* 10:23-30, 201, 2018

- Blossom, S.J., Fernandes, L., Bai, S., Chare, S., Gokulan, K., Yuan, Y., Dewall, M., Simmen, F.A., and **Gilbert, K.M**., Opposing actions of developmental toxicity and high-fat diet coexposure on markers of lipogenesis and inflammation in autoimmune-prone mice, *Toxicological Science*, 164:313-327, 2018.
- **Gilbert, K.M**., Blossom, S.J., Reisfeld, B., Erickson, S.W., Vyas, K., Maher, M. Broadfoot, B., West, K., Bai, S., Cooney, C.A., and Bhattacharyya, S., Trichloroethylene-induced alterations in DNA methylation were enriched in polycomb protein binding sites in effector/memory CD4+ T cells, *Environmental Epigenetics* 3. Epub 2017.
- Frye, R.E., Rose, S., Wynne, R., Bennuri, S.C., Blossom, S., **Gilbert, K.M**., Heilbrun, L., and Palmer, R.F., Oxidative stress challenge uncovers trichloracetaldehyde hydrate-induced mitoplasticity in autistic and control lymphoblastoid cell lines, *Science Report* 7:4478, 2017.
- **Gilbert, K.M**., Bai, S., Barnette, D., and Blossom, S.J. Exposure cessation during adulthood did not prevent immunotoxicity caused by developmental exposure to low-level trichloroethylene in drinking water. *Toxicological Science* 157: 429-437, 2017
- Meadows, J.R., Parker, C., **Gilbert, K.M**., Blossom, S.J., and Dewitt, J.C., A single dose of trichloroethylene given during development does not substantially alter markers of neuroinflammation in brains of adult mice. *Immunotoxicology* 14:95-102, 2017.
- **Gilbert, K.M.**, Blossom, S.J., Erickson, S.W., Broadfoot, B., West, K., Bai, S. and Cooney, C.A. Chronic exposure to trichloroethylene increases DNA methylation of the ifng promoter in $CD4^+$ T cells. *Toxicology Letters*, 260:1-7, 2016.
- **Gilbert, K.M.**, Blossom, S.J., Erickson, S.W., Reisfeld, B., Zurlinden T.J., Broadfoot, B., West, K., Bai, S. and Cooney, C.A. Chronic exposure to water pollutant trichloroethylene increased epigenetic drift in $CD4^+$ T cells. *Epigenomics*, 8:633-649, 2016.
- **Gilbert, K.M.**, Reisfeld, B., Zurlinden T.J., Kreps, M.N., Erickson, S.W. and Blossom, S.J. Modeling toxicodynamic effects of trichloroethylene on liver in mouse model of autoimmune hepatitis. *Toxicology and Applied Pharmacology*, 279:284-293, 2014.
- **Gilbert, K.M**., Woodruff, W. and Blossom, S.J., Differential Immunotoxicity induced by two different windows of developmental trichloroethylene exposure, *Autoimmune Diseases.* Epub 2014
- **Gilbert, K.M**. Autoimmunity Hepatitis. *Encyclopedic Reference of Immunotoxicology,* Vohr, Hans-Wener (Ed), Springer Publishing Co., 2013.
- Blossom S.J., Melnyk, S., Cooney C.A., **Gilbert K.M.**, and James, S.J. Postnatal exposure to trichloroethylene alters glutathione redox homeostasis, methylation potential, and neurotrophin expression in the mouse hippocampus. *Neurotoxicology*. 127:169-178, 2012.
- Fontenelle, B. and **Gilbert, K.M.,** n-Butyrate anergized effector CD4+ T cells independent of regulatory T cell generation or activity, *Scandinavian Journal of Immunology*, 76:457-463, 2012.
- **Gilbert, K.M.**, Nelson, A.R, Cooney, C.A., Reisfeld, B., and Blossom, S.J. Epigenetic alterations may regulate temporary reversal of $CD4^+$ T cell activation

caused by trichloroethylene exposure. *Toxicological Sciences*. 127:169-178, 2012.

- **Gilbert, K.M.,** Rowley, B, and Blossom, S.J, Co-exposure to $HgCl_2$ increases immunotoxicity of trichloroethylene, *Toxicological Sciences*, 119: 281-292, 2011.
- **Gilbert, K.M**. Xenobiotic exposure and Autoimmune Hepatitis. *Hepatitis Research and Treatment*, 2010:248157, 10 pages, 2010.
- Dagtas, A.S. and **Gilbert, K.M**., $p21^{CIP1}$ upregulated during histone deacetylase inhibitor-induced CD4+ T cell anergy selectively associates with MAPKs, *Immunology*, 129: 589-599, 2010.
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Book Chapters:

- **Gilbert, K.M**. *Trichloroethylene and Autoimmunity in Human and Animal Models* in Trichloroethylene: Toxicity and Health Risks, Edited by **Gilbert, K.M** and Blossom, S.J. Springer. 15-36, 2014.
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Platform presentations

- **Gilbert, K.M.** Autoimmune-prone versus normal mice as models for toxicant-mediated autoimmune disease. In Workshop: Strengths and weaknesses of mice as a model for humans in studies of immunological effects of drugs and chemicals , Society of Toxicology, San Diego, March, 2015.
- **Gilbert, K.M**. Trichloroethylene exposure and epigenetic alterations in T cell function. In Prenatal Programming and Toxicity IV, Boston, MA, October, 2014
- **Gilbert, K.M**. Autoimmune disease triggered by trichloroethylene is associated with epigenetic alterations in $CD4^+$ T cells." In Environmental Health 2013, Science and Policy to Protect Future Generations, Boston, MA, March, 2013
- **Gilbert, K.M**. Chronic exposure to water pollutant trichloroethylene promotes autoimmune hepatitis and induces epigenetic alterations in $CD4^+$ T cells. In Symposium entitled "Role of Environmental Exposures in the Development of Autoimmune Disease", The American Association of Immunologists Annual Meeting, Boston, MA, 2012.
- **Gilbert, K.M**. Environmental pollutants that trigger immune dysfunction and promote autoimmune disease. Keynote speaker at FDA's National Center for Toxicological Research Office of Women's Health Research Update Program, August 10, 2012.
- **Gilbert, K.M**. Trichloroethylene-induced autoimmunity; dependence on metabolism and genetic susceptibility, In Workshop entitled "Autoimmunity

versus systemic hypersensitivity: commonalities useful for toxicity testing", Society of Toxicology Annual Meeting, 2011.

- **Gilbert, K.M**., Rowley, B., Hennings, L., and Blossom, S.J. Co-exposure to mercury accelerates autoimmunity induced by trichloroethylene, NCTR Women's Health Research Workshop, Little Rock, September, 2010.
- **Gilbert, K.M**., Rowley, B., Hennings, L., and Blossom, S.J. Mice exposed to a binary mixture of immunotoxicants developed unique autoimmune effects not induced by single exposure, 49th Society of Toxicology Annual Meeting, Salt Lake City, Utah, March, 2010.
- **Gilbert, K.M.,** Przybyla, B., Pumford, N.R., Han, T, Fuscoe, J., Schnackenberg, L.K., Holland, R.D., Doss, J.C. MacMillan-Crow, L, and Blossom, S.J. Combining transcriptomics and metabolomics to delineate immunotoxicity of trichloroethylene, NSF Advance Program Planning meeting, Petit Jean, AR, March, 2009.
- **Gilbert, K.M.,** Yeung, S., Nelson, A., and Przybyla, B., Susceptibility factors in trichloroethylene-induced autoimmunity, South Central Society of Toxicology annual meeting, NCTR, Jefferson, AR, September, 2008.
- **Gilbert, K.M**., Whitlow, A.B., and Pumford, N.R., Environmental toxicant associated with the development of autoimmune disease stimulates T cell signaling, Environmental Factors in Autoimmune Disease, NIEHS, Durham, NC, February, 2003.
- **Gilbert, K.M**., Whitlow, A.B. and Pumford, N.R. Environmental contaminant associated with induction of autoimmune disease stimulates T cells via Schiff base formation, American Association of Immunologists Annual Meeting, New Orleans, LA, April, 2002.
- **Gilbert, K.M**., Fecher, N.B., Freeman, J.P., Wahid, R. and Fifer, E.K. Potential clinical use of butyric acid prodrugs to induce antigen-specific T cell inactivation. American Association of Immunologists Annual Meeting, Seattle, May, 2000.
- **Gilbert, K.M**., M.L. Thoman, K. Bauche, and Weigle, W.O., TGF-β1-induced tolerance in antigen-specific naïve T cells, The 9th International Congress of Immunology, San Francisco, July, 1995.
- **Gilbert, K.M.** and Weigle, W.O. Use of G1a blockers to induce antigen-specific T cell anergy, New Strategies for Selective Immune Suppression, Cambridge Healthtech Institute, Waltham, MA, October, 1994.
- **Gilbert, K.M.,** and Weigle, W.O., Activated B cells which express CTLA-4 counter-receptors are tolerogenic. American Association of Immunologists Annual Meeting, Anaheim, April, 1994.
- **Gilbert**, **K.M.** and Weigle, W.O., Activation does not reverse B cell tolerogenicity, American Association of Immunologists Annual Meeting, May, Denver, CO, 1993.
- **Gilbert, K.M.,** Hobbs, M.V. Ernst, D.N., and Weigle, W.O., Heterogeneity in the ability of different antigen presenting cells to tolerize Th1 and Th2 clones, American Association of Immunologists Annual Meeting, 1992.
- **Gilbert, K.M.** Effects of tolerance induction on cell cycle progression by the Th1 and Th2 clones, 18th Annual Conference of the La Jolla Immunologists, San Diego, CA, 1991.

- **Gilbert, K.M**. Hoang, K.D. and Weigle, W.O., Tolerized high density Th clones lose bystander helper activity, American Association of Immunologists Annual Meeting, April, 1989.
- **Gilbert, K.M.** and Weigle, W.O. B cell activation by T helper cells. MidWinter Conference of Immunologists, Asilomar, CA., 1988.
- **Gilbert**, **K.M.** and Hoffmann, M.K. cAMP as a 2nd messenger in antibody production by B cells. American Association of Immunologists Annual Meeting, Anaheim, April, 1985.

- **Sessions Chaired:**

- "Epigenetics" as Presented at the 51st Annual Society of Toxicology meeting, San Francisco, CA, March, 2012.
- Platform Session "Developmental Immunotoxicology, Host Resistance and Genomics, Society of Toxicology Meeting, Seattle, 2008.
- Platform Session "Immunotoxicity" Society of Toxicology Annual Meeting, San Diego, CA, 2006.
- Co-chaired Symposia "T cell inactivation and apoptosis", American Association of Immunologists Annual Meeting, San Francisco, April, 1998.
- Co-chaired Immunology session for American Society of Microbiology, South Central Branch, Little Rock, AR, 1995
- Co-chaired Symposium "T cell tolerance and anergy", American Association of Immunologists Annual Meeting, Anaheim, CA, April, 1994.
- Co-chaired Symposium "T cell regulation," American Association of Immunologists Annual Meeting, May, Denver, CO, 1993.

- **Other Invited Presentations:**

- "Environmental pollutants as triggers of autoimmune disease" Distinguished Speaker, Environmental Health Sciences, University of Michigan School of Public Health, Ann Arbor, MI, April 22, 2015.
- "Trichloroethylene as a trigger of autoimmune disease." In Society for Women's Health Research Autoimmune Disease Roundtable, Washington, D.C., October 5, 2012.
- Trichloroethylene-induced autoimmunity; dependence on metabolism and genetic susceptibility, In Workshop entitled "Autoimmunity versus systemic hypersensitivity: commonalities useful for toxicity testing, Society of Toxicology Annual Meeting, 2011.
- Developing an immunotoxicology center in Arkansas, Arkansas Biosciences Institute Fall Research Symposium, Little Rock, AR, September, 2010.
- Co-exposure to mercury accelerates autoimmunity induced by trichloroethylene, International Congress of Toxicology, Barcelona, Spain, July, 2010.

- Developing an immunotoxicity center in Arkansas, Arkansas Children's Hospital Research Institute Board, May, 2010.
- Environmental pollutants as triggers for autoimmune disease, South Central Branch ASM, Nicholls State University in Thibodaux, LA, November 2009.
- Contribution of environmental pollutants to autoimmune disease, Jones Eye Center Seminar Series, Little Rock, AR, June 2008.
- Combining transcriptomics and metabolomics to delineate immunotoxicity of trichloroethylene, Society of Toxicology Annual Meeting, Seattle, WA, March, 2008.
- Histone deacetylase inhibitors block MAP kinases to induce tolerance in Th1 cells, The University of Pennsylvania School of Medicine, Department of Pathology and Laboratory Medicine, Division of Transplantation Immunology Seminar Series, Philadelphia, PA, May 16, 2007
- Examining the genetic susceptibility to the immunotoxicity of a trichloroethylene metabolite, Society of Toxicology Annual Meeting, Charlotte, NC, March, 2007.
- Distinguished Speaker: Environmental contaminant and Superfund chemical trichloroethylene promotes autoimmune disease and inhibits T cell apoptosis", Bench to Bedside Symposium: Immunomodulation by Environmental Factors: The role of the Environment in Autoimmune Disease, Center for Immunopathology and Microbial Pathogenesis, Morgantown, West Virginia, December, 2006.
- Environmental contaminant trichloroethylene promotes autoimmune disease and inhibits T cell apoptosis, Society of Toxicology Annual Meeting, San Diego, CA, March, 2006.
- Contribution of environmental contaminants to autoimmune disease, Workshop on Lupus and the Environment: Disease Development, Progression and Flares, NIEHS, Washington, DC, September, 2005.
- The environmental toxicant trichloracetaldehyde promotes activation and inhibits apoptosis of mature T lymphocytes by inhibiting fas ligand expression, 12th International Congress of Immunology, Montreal, Canada, 2004.
- Butyric acid derivative induces allospecific T cell tolerance, Arthritis Foundation Research Conference, Keystone Resort, Colorado, June, 2003
- Why you should go with the flow; new research applications for flow cytometry, Okie-Arkie Bi-State Meeting, Little Rock, Arkansas, April, 2003
- Novel G1 blocker inhibits antigen-specific T cell response and prevents graft-versus-host disease, Arkansas Biosciences Institute Fall Research Symposium, Little Rock, AR 2002
- Autoimmunity, Research Council, College of Medicine, UAMS. Research Retreat I, Advancing collaborative research and funding strategies, Little Rock, AR, 2001
- Why you should go with the flow, Pharmaceutical Sciences Seminar, UAMS, 2001
- T cell anergy linked to alterations in cell cycle regulatory proteins. American Association of Immunologists Annual Meeting, San Francisco, April, 1998.
- G1 blockers induce anergy in CD4^{+}T cells, American Association of Immunologists Annual Meeting, New Orleans, LA., June, 1996.

- T cell tolerance as immunotherapy, Hematology Oncology Research Seminar Series, Arkansas Cancer Research Center, November, 1995
- Activated B cells which express CTLA-4 counter-receptors are tolerogenic, American Association of Immunologists Annual Meeting, Anaheim, CA, April, 1994.
- Use of G1 blockers to induce Th cell anergy, Glaxo Institute for Molecular Biology, Geneva, Switzerland, January, 1994.
- T cell tolerance, American Association of Immunologists Annual Meeting, Anaheim, CA, April, 1992.
- Effects of tolerance induction on cell cycle progression by the Th1 and Th2 clones, Annual Conference of La Jolla Immunologists, La, Jolla, CA, November, 1991.

Other abstracts/posters presentations:

- Zurlinden, TJ, **Gilbert, KM**, and Reisfeld,B. A computational approach for characterizing subtle changes in DNA methylation in $CD4^+$ T cells. FutureTox III, Arlington, VA, November, 2015.
- **Gilbert, KM**, Cooney, C , Broadfoot, B., Chandler, G. and Blossom, SJ. Long-term exposure to water pollutant trichloroethylene increased plasticity of DNA methylation in *Ifng* promoter and induced non-monotonic *Ifng* expression in effector/memory $CD4^+$ T cells, Gordon Conference Cellular & Molecular Mechanisms of Toxicity, Andover, NH, 2015.
- **Gilbert, KM**, Cooney, C., and Blossom, S. Autoimmune disease triggered by trichloroethylene is associated with epigenetic alterations in $CD4^+$ T cells, 52^{nd} Annual Society of Toxicology meeting, San Antonio, Texas, March, 2013.
- **Gilbert, KM**, Nelson, A., Cooney, C., and Blossom, S. Subchronic trichloroethylene exposure alters epigenetic processes in $CD4^+$ T cells, 51^{st} Annual Society of Toxicology meeting, San Francisco, CA, March, 2012.
- Blossom, SJ, Melnyk, **Gilbert, KM,** and James, J. Postnatal trichloroethylene modulates redox status and oxidative stress in mouse hippocampus, 51^{st} Annual Society of Toxicology meeting, San Francisco, CA, March, 2012.
- Blossom, SJ, Melnyk, S, **Gilbert, KM**, James SJ. Differential Expression of Neuroimmune Mediators Following Postnatal Exposure to Trichloroethylene. The 27^{th} International Neurotoxicology Conference; Environmentally Triggered Neurodevelopmental Disorders: Focus on Endocrine Disruption and Sex Differences in Autism, ADHD, and Schizophrenia, Research Triangle Park, NC**.** October 30-November 2, 2011.
- Blossom SJ, Melnyk S, **Gilbert KM**, James SJ. Altered Redox Status and Oxidative Stress in Hippocampus of Mice Postnatally Exposed to Trichloroethylene, Arkansas Biosciences Institute Fall Research Symposium, September 21, 2011.
- Blossom SJ, Melnyk S, **Gilbert KM**, James SJ. Maternal and early life trichloroethylene exposure modulates gene expression of chemokines and

neurotrophins in the brain, 50th Annual Society of Toxicology meeting, Washington DC. March 10, 2011.

- Blossom SJ, Melnyk S, **Gilbert KM**, James SJ. Neuroimmune dysregulation with developmental exposure to trichloroethylene in a mouse model relevant to neurodevelopmental disorders, Arkansas Biosciences Institute Fall Research Symposium, Little Rock, AR. September 29. 2010.
- **Gilbert, K.M.,** Boger,S., Fifer, and Price, P. T cell tolerance induced by novel G1 blocker is mediated by cyclin-dependent kinase inhibitor p21cip1, 12th International Congress of Immunology, Montreal, Canada, 2004.
- Blossom, S.J., and **Gilbert, K.M**. Trichloroethylene-induced autoimmunity, Environmental Factors in Autoimmune Disease, NIEHS, Durham, NC, February, 2003.
- **Gilbert, K.M**., DeLoose, A., and Jackson, S.K. n-Butyrate-induced Th1 cell anergy associated with $p21^{Cip1}$ inhibition of MAPK pathway. American Association of Immunologists Annual Meeting, New Orleans, LA, April, 2002.
- **Gilbert, K.M**., Jackson, S.K., and DeLoose, A. Th1 cell anergy is associated with increased levels of both $p21^{Cip1}$ and $p27^{Kip1}$. American Association of Immunologists Annual Meeting, Orlando, FL, April, 2001.
- Brand, K.A., **Gilbert, K.M**., Yingyun, C., E. Kim Fifer, E.K., Synthesis of butyric acid derivatives as immune response modulators. Western Region Merck Pharmacy Research Seminar, Denver, CO, June, 2001.
- Jackson, S.K. and **Gilbert, K.M**. Anergy induction in Th1 cells increases expression of cyclin-dependent kinase inhibitors. American Association of Immunologists Annual Meeting, Seattle, May, 2000.
- **Gilbert, K.M**. and Blossom, S.J. B cells from autoimmune BXSB mice are hypo-responsive to signals provided by CD4+ T cells. American Association of Immunologists Annual Meeting, Seattle, May, 2000.
- Griffin, J.M., **Gilbert, K.M**., and Pumford, N.R. Trichloroethylene accelerates an autoimmune response in MRL+/+ mice at doses similar to human exposure levels. Society of Toxicology, New Orleans, La, March, 1999.
- Fecher, N.I.P., **Gilbert, K.M.** Wahid, R. and Fifer, E.K., Butyric acid prodrugs as modulators of immune response. Western Region Merck Undergraduate Pharmacy Research Seminar", University of Colorado School of Pharmacy, Denver, CO, June, 1999.
- Blossom, S. Chu, E.B., Weigle, W.O. and **Gilbert, K.M**. B cells from autoimmune BXSB mice express CD40 ligand. American Association of Immunologists Annual Meeting, San Francisco, April, 1998
- Griffin, J.M., **Gilbert, K.M.,** and Pumford, N.R. Cytochrome P450 2E1 activation of trichloroethylene initiates a Th_1 T cell response in MRL+/+ mice. Linking Environmental Agents and Autoimmune Diseases, National Institutes of Environmental Health and Safety, 1998.
- Griffin, J.M., **Gilbert, K.M**., and Pumford, N.R. Acceleration of an autoimmune response in MRL+/+ mice exposed to trichloroethylene at doses similar to human exposure levels. South Central Society of Toxicology, 1998.
- Griffin, J.M**.,** Wong, J., Blossom, S.M., Jackson, S.K., **Gilbert, K.M**., and Pumford, N.R., Immunomodulation induced by trichloroethylene-in the

autoimmune prone MRL+/+ mice. Society of Toxicology, Seattle, WA, March, 1998.

- Blossom, S. and **Gilbert, K.M.** B cells from autoimmune BXSB mice express CD40 ligand. UAMS Student Research Day, Won second prize for best graduate student presentation, April, 1997.
- Blossom, S., Chu, E.B., Weigle, W.O., and **Gilbert, K.M**. , Role of CD40L+ B cells in autoimmune BXSB mice, SLE Foundation annual meeting, National Institute of Health, November, 1997.
- Griffin, J.M., **Gilbert, K.M**., and Pumford, N.R. Trichloroethylene-induced autoimmunity in MRL/++ mice, South Central Chapter of the Society of Toxicology, Jefferson, AR, November, 1997.
- Blossom, S., **K.M. Gilbert**, Increased expression of costimulator molecules on antigen presenting cells in the BXSB mouse model of systemic lupus erythematosus, American Association of Immunologists Annual Meeting, New Orleans, LA, June, 1996.
- Blossom, S. and **Gilbert, K.M**. Irregular expression of costimulator molecules on antigen presenting cells in the BXSB mouse model of systemic lupus erythematosus, American Society of Microbiology, South Central Branch, Little Rock, AR, November, 1995.
- Weigle, and **Gilbert, K.M**., Th1 cell anergy and G1a blockade. American Association of Immunologists Annual Meeting, May, Denver, CO, 1993.
- **Gilbert**, **K.M.,** Ernst, D.N., Hobbs, M.V., and Weigle, W.O. Cell cycle progression by tolerized Th1 and Th2 clones. American Association of Immunologists Annual Meeting, Anaheim, April, 1992.
- Rothermel, A.L., Ernst, D.N., Hobbs, M.V., Weigle, W.O., and **Gilbert, K.M.** Ability of tolerized Th1 and Th2 clones to stimulate B cell activation and cell cycle progression. American Association of Immunologists Annual Meeting, Anaheim, April, 1992.
- Rothermel, A.L., **Gilbert, K.M.** and Weigle, W.O., Induction of polyclonal B cell proliferation by activated T helper cells and their lymphokines, American Association of Immunologists Annual Meeting, April, 1989.

LEADERSHIP

Examples of Leadership Roles at UAMS

Role	Responsibility	Affiliation	Years
Director	Arkansas Center for Environmental Exposure Research: ACEER was initiated in 2002, and since then received over 3 million dollars in extramural grant support from the NIH and other sources, and 1.6 million dollars in intramural support from the Arkansas Biosciences Institute. It provided salary and/or infrastructure support to recruit and/or retain 10 faculty members and 20 undergraduate and graduate students in 5 institutions around the state, thus enabling them to work together on common issues concerning environmental contamination and remediation.	UAMS/ACHRI	2002 - 2017
President	Women's Faculty Development Caucus (WFDC)	UAMS	2005 - 2007
Co-Director and then on organizing committee	**UAMS Graduate School Career Day**. Current graduate students, and undergraduates from all over Arkansas and surrounding states visit UAMS to hear about our graduate program, and to learn about career opportunities for PhDs.	UAMS	2002 - 2017

PROFESSIONAL RECOGNITION/ADVOCACY FOR WORK WITH TCE

- 2005: Participated in National Institutes of Health Workshop on Lupus & the Environment; Disease Development, Progression and Flares. I represented the work done on solvents and autoimmune disease at this workshop organized by the NIH to develop grant funding on the subject of environmental pollutants and the development of lupus.
- 2006: Consulted with the Committee on Human Health Risks of Trichloroethylene, National Research Council during the development of document entitled *Assessing the Human Health Risks of Trichloroethylene: Key Scientific Issues*,
- 2007: Consulted with Pew Charitable Trust Environmental Working Group for "Kid-Safe Chemicals Act of 2008" bill before US Congress.

- 2008: Featured in *The Autoimmune Epidemic* by Donna Jackson Nakazawa, Simon & Schuster, New York
- 2008: Featured in "The Scariest Health Threat You've Never Heard Of" in *Glamour*, September
- 2009: Participated in the EPA Science Advisory Board's review of the Trichloroethylene (TCE) health assessment
- 2013: Served on an expert panel that reviewed EPA TSCA Workplan Chemical Risk Assessment for Trichloroethylene: Degreaser and Arts/Crafts Uses
- 2014: Served on a TCE Information Group tasked with assisting the NTP Office of the Report on Carcinogens as they considered a possible change in listing status for TCE in the Report on Carcinogens. Specifically, we were asked to provide comments on whether the information concerning the immunotoxicity of TCE provided biological plausibility for TCE-related cancers.
- 2014: Worked with the Arkansas Department of Environmental Quality and the Arkansas Department Health to identify TCE-contaminated sites in Northern Arkansas, and to identify toxicant-induced autoimmune disease in people living near the sites
- 2017: Selected as a permanent member of the Scientific Advisory Committee on Chemicals (SACC) (Toxic Substances Control Act), for the US Environmental Protection Agency. The SACC is tasked with providing independent advice and expert consultation on issues related to the implementation of the Frank R. Lautenberg Chemical Safety for the 21st Century Act which amends the Toxic Substances Control Act. The first 10 chemicals reviewed included trichloroethylene, tetrachloroethylene (perchloroethylene), carbon tetrachloride, methylene chloride, 1-bromopropane, n-methyl pyrrolidone, 1,4-dioxane, pigment violet 29, asbestos, and cyclic aliphatic bromide cluster.
- 2019: As requested by the National Academy of Sciences reviewed a report prepared by the National Academies Board on Environmental Studies and Toxicology concerning their review of the *DOD's Approach to Deriving an Occupational Exposure Level for Trichloroethylene*

LITIGATION HISTORY

Case	Law Firm	Contribution	Outcome
Jodelle L. Kirk v Schaeffler Group USA Inc.: FAG Bearings, LLC, 2016 United States District Court Western District of Missouri, Cause No 3:13-cv-0503	Humphrey, Farrington, & McClain	Wrote expert report on TCE Deposed Testified at trial as to general and specific causation	Plaintiff awarded $20.6 million dollars
Hostetler, et al. vs Johnson Co, Inc, et al. 2018 United Stated District Court Northern District of Indiana Cause No. 3:15-CV-226JD-MGG	Taft Stettinius & Hollister LLP	Wrote expert report on TCE general causation increasing risk for autoimmune diseases and cancer Deposed	Settled in 2023
Asher, et al. v Raytheon Technologies Co, et al. Huntington Superior Court State of Indiana Cause No. 35D-01-2006-CT-000338 Emergency hearing to determine health risks of the drinking water in Andrews, Indiana, 2020	Taft Stettinius & Hollister LLP	Wrote Affidavit concerning human health effects of vinyl chloride and cis-1,2-Dichloroethylene in water supply Testified at remote hearing Deposed 4-16-24	Emergency action was denied
Millman, Powell and Powell vs Raytheon Technologies F/k/a United Technologies et al. Corporation, 2021 Northern District of Indiana Cause No.:1:16-cv-00312-HAB-SLC	Taft Stettinius & Hollister LLP	Wrote expert report on human health effects of trichloroethylene, vinyl chloride, benzene, and cis-1,2-Dichloroethylene Performed risk assessments for 3 plaintiffs Opinioned that toxicant exposure contributed to development of liver cancer and trigeminal neuralgia in 2 plaintiffs Deposed	Ongoing

Houlihan vs United Technologies Corporation, 2019 Huntington Superior Court State of Indiana Cause No. 35C01-1803-CT-000144	Taft Stettinius & Hollister LLP	Wrote expert report on the ability of trichloroethylene, vinyl chloride and benzene to promote immunotoxicity and cancer Deposed	Ongoing
Funderburk et al. vs Johnson Controls, Inc. and TOCON Holdings, LLC, 2021	Taft Stettinius & Hollister LLP	Wrote expert report concerning the human health effects of trichloroethylene, perchloroethylene, vinyl chloride and cis-1,2-Dichloroethylene Performed risk assessments for 94 plaintiffs Deposed 8-30-23	Ongoing
Taylor et al. v Schaeffler Group., et al (Case No.:20AO-CC0341)	Humphrey, Farrington & McClain Independence, Missouri	Trichloroethylene general causation Deposed 5-17-23	
Preliminary research, 2022	Mueller Law Offices, Austin Texas	Generated report on epidemiological studies linking trichloroethylene exposure and human health	
Preliminary research, 2022	Romanucci & Blandin, Chicago, IL	Performed risk assessments for 19 plaintiffs	

Appendix B

Fee Schedule

Kathleen M. Gilbert, PhD
Immunotoxicologist

(501) 249-4552
gilbertkathleenm4@gmail.com

240 West 75th St, Apt. 1B, New York, NY 10023
800 Shire Court, Fort Collins, CO 80526

- Hourly charge for document and record review: $400
- Hourly charge for consulting over the phone: $250
- Hourly charge for affidavit/report writing: $450
- Hourly charge for deposition: $500
- Hourly charge for trial testimony: $500

DR. GILBERT'S RELIANCE FILES

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF NORTH CAROLINA
SOUTHERN DIVISION

IN RE:	)	
	)	
CAMP LEJEUNE WATER LITIGATION	)	
	)	
This Document Relates to:	)	Case Nos.:
	)	
ALL CASES	)	7:23-CV-897
	)	
DAVID DOWNS	)	7:23-CV-01145-BO
	)	
DAVID WILLIAM FANCHER	)	7:23-CV-00275-BO-BM
	)	
ALLAN WAYNE HOWARD	)	7:23-CV-00490-BO
	)	
FRANK W. MOUSSER	)	7:23-CV-00667-BO-RN
	)	
JACQUELINE JORDAN TUKES	)	7:23-CV-01553-BO-BM

PLAINTIFFS' DESIGNATION AND DISCLOSURE OF PHASE II EXPERT WITNESSES WITH RESPECT TO KIDNEY CANCER

KATHLEEN M. GILBERT, PhD'S RELIANCE FILES

Pursuant to Fed. R. Civ. P. 26(a)(2)(B)(ii) and the Stipulated Order Regarding Expert Discovery (Case Management Order No. 17) (D.E. 305), Plaintiffs hereby identify the facts, data, and publications considered by Kathleen M. Gilbert ("Dr. Gilbert") in forming her opinions concerning general causation and kidney cancer.

Dr. Gilbert's report, produced contemporaneously herewith, contains a thorough statement of the facts, data, and publications that she considered in forming his opinions, including an extensive section entitled "References," and Plaintiffs incorporate all facts, data, and publications referenced in Dr. Gilbert's report as if fully listed herein. In addition, Plaintiffs identify the following facts, data, and publications considered by Dr. Gilbert in forming her opinions:

1. Bove FJ, Ruckart PZ, Maslia M, Larson TC. Evaluation of mortality among marines and navy personnel exposed to contaminated drinking water at USMC base Camp Lejeune: a retrospective cohort study. Environ Health. 2014 Feb 19 (bates number CLJA_HEALTHEFFECTS-0000141103);

2. Bove FJ, Ruckart PZ, Maslia M, Larson TC. Mortality study of civilian employees exposed to contaminated drinking water at USMC Base Camp Lejeune: a retrospective cohort study. Environ Health. 2014 Aug 13 (bates number CLJA_VA_RFP_4THSET_0000135084));

3. ATSDR Public Health Assessment, 2017 (bates number CLJA_HEALTHEFFECTS-0000000011);

4. ATSDR Assessment of the Evidence for the Drinking Water Contaminants at Camp Lejeune and Specific Cancers and Other Diseases, 2017 (bates number CLJA_VA-RFP11-0000000131);

5. ATSDR. Morbidity Study of Former Marines, Employees, and Dependents Potentially Exposed to Contaminated Drinking Water at U.S. Marine Corps Base Camp Lejeune, April 2018 (bates number CLJA_HEALTHEFFECTS-0000000214);

6. Bove FJ, Greek A, Gatiba R, Kohler B, Sherman R, Shin GT, Bernstein A. Cancer Incidence among Marines and Navy Personnel and Civilian Workers Exposed to Industrial Solvents in Drinking Water at US Marine Corps Base Camp Lejeune: A Cohort Study. Environ Health Perspect. 2024 Oct;

7. Bove FJ. Evaluation of cancer incidence among Marines and Navy personnel and civilian workers exposed to contaminated drinking water at USMC Base Camp Lejeune: a cohort study (Unpublished). 2024 Jan 29 (bates number CLJA_ATSDR_BOVE-0000060101);

8. Bove FJ, Greek A, Gatiba R, Boehm RC, Mohnsen MM. Evaluation of mortality among Marines, Navy personnel, and civilian workers exposed to contaminated drinking water at USMC base Camp Lejeune: a cohort study. Environ Health. 2024 Jul 3;

9. Andrew AS, Li M, Shi X, Rees JR, Craver KM, Petali JM. Kidney Cancer Risk Associated with Historic Groundwater Trichloroethylene Contamination. Int J Environ Res Public Health. 2022 Jan 6;

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11. Webler T, Brown HS. Exposure to tetrachloroethylene via contaminated drinking water pipes in Massachusetts: a predictive model. Arch Environ Health. 1993 Sep-Oct;

12. Aschengrau A, Gallagher LE, Webster TF, Heeren TC, Ozonoff DM. Evaluation of the Webler-Brown model for estimating tetrachloroethylene exposure from vinyl-lined asbestos-cement pipes. Environ Health. 2008 Jun 2;

13. Alanee S, Clemons J, Zahnd W, Sadowski D, Dynda D. Trichloroethylene Is Associated with Kidney Cancer Mortality: A Population-based Analysis. Anticancer Res. 2015 Jul

14. Fagliano J, Berry M, Bove F, Burke T. Drinking water contamination and the incidence of leukemia: an ecologic study. Am J Public Health. 1990 Oct;

15. Moore LE, Boffetta P, Karami S, Brennan P, Stewart PS, Hung R, Zaridze D, Matveev V, Janout V, Kollarova H, Bencko V, Navratilova M, Szeszenia-Dabrowska N, Mates D, Gromiec J, Holcatova I, Merino M, Chanock S, Chow WH, Rothman N. Occupational trichloroethylene exposure and renal carcinoma risk: evidence of genetic susceptibility by reductive metabolism gene variants. Cancer Res. 2010 Aug 15;

16. Parker S, Rosen S. Woburn: Cancer Incidence and Environmental Hazards 1969-1978. 1981 Jan 23;

17. Rosenfeld P, Spaeth K, McCarthy S, Winter S, Wilson M, Hagemann M. Camp Lejeune Marine Cancer Risk Assessment for Exposure to Contaminated Drinking Water from 1955 to 1987. 2023 Mar 21;

18. Lynge E, Andersen A, Nilsson R, Barlow L, Pukkala E, Nordlinder R, Boffetta P, Grandjean P, Heikkilä P, Hörte LG, Jakobsson R, Lundberg I, Moen B, Partanen T, Riise T. Risk of cancer and exposure to gasoline vapors. Am J Epidemiol. 1997 Mar 1;

19. Collins JJ, Anteau SE, Swaen GM, Bodner KM, Bodnar CM. Lymphatic and hematopoietic cancers among benzene-exposed workers. J Occup Environ Med. 2015 Feb;

20. Gérin M, Siemiatycki J, Désy M, Krewski D. Associations between several sites of cancer and occupational exposure to benzene, toluene, xylene, and styrene: results of a case-control study in Montreal. Am J Ind Med. 1998 Aug;

21. Pesch B, Haerting J, Ranft U, Klimpel A, Oelschlägel B, Schill W, MURC Study Group. Occupational risk factors for urothelial carcinoma: agent-specific results from a case-control study in Germany. 2000;

22. Hu J, Mao Y, White K. Renal cell carcinoma and occupational exposure to chemicals in Canada. Occup Med (Lond). 2002 May;

23. Purdue MP, Stewart PA, Friesen MC, Colt JS, Locke SJ, Hein MJ, Waters MA, Graubard BI, Davis F, Ruterbusch J, Schwartz K, Chow WH, Rothman N, Hofmann JN. Occupational exposure to chlorinated solvents and kidney cancer: a case-control study. Occup Environ Med. 2017 Mar;

24. Vandenberg L, et al. Addressing systemic problems with exposure assessments to protect the public's health 2022;

25. EPA. Toxicological Review of Trichloroethylene. 2011 Sep;

26. ATSDR. Toxicological Profile for Trichlorethylene 2019 Jun;

27. Water Modeling Data – Appendices I, J, H1 & K to Morris Malia's report in the above-captioned matter, dated October 25, 2024;

28. Deposition of Frank Bove;

29. Deposition of Morris Maslia;

30. The Camp Lejeune Justice Act;

31. All facts and data listed herein are either identified by bates number or are publicly available to and accessible by Defendant United States of America;

32. Dr. Gilbert reserves the right to review and consider additional facts, data and publications;

33. Dr. Gilbert reserves the right to consider the report of any other witness in this action; and

34. Dr. Gilbert reserves the right to supplement this list of reliance files.